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(54) Title: MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

(57) Abstract: Human MBCAT genes are identified as modulators of the beta-catenin pathway, and thus are therapeutic targets for disorders associated with defective beta-catenin function. Methods for identifying modulators of beta-catenin, comprising screening for agents that modulate the activity of MBCAT are provided.



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MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

REFERENCE TO RELATED APPLICATIONS

5 This application claims priority to U.S. provisional patent applications 60/454,469 filed 3/13/2003, 60/470,728 filed 5/14/2003, 60/479,795 filed 6/19/2003, and 60/479,769 filed 6/19/2003. The contents of the prior applications are hereby incorporated in their entirety.

BACKGROUND OF THE INVENTION

10 The *Drosophila Melanogaster* Armadillo/beta-catenin protein is implicated in multiple cellular functions. The protein functions in cell signaling via the Wingless (Wg)/Wnt signaling pathway. It also functions as a cell adhesion protein at the cell membrane in a complex with E-cadherin and alpha-catenin (Cox et al. (1996) J. Cell Biol. 134: 133-148; Godt and Tepass (1998) Nature 395: 387-391; White et al. (1998) J Cell biol. 140:183-195). These two roles of beta -catenin can be separated from each other (Orsulic and Peifer (1996) J. Cell Biol. 134: 1283-1300; Sanson et al. (1996) Nature 383: 627-630).

20 In Wingless cell signaling, beta -catenin levels are tightly regulated by a complex containing APC, Axin, and GSK3 beta /SGG/ZW3 (Peifer et al. (1994) Development 120: 369-380).

25 The Wingless/ beta -catenin signaling pathway is frequently mutated in human cancers, particularly those of the colon. Mutations in the tumor suppressor gene APC, as well as point mutations in beta -catenin itself lead to the stabilization of the beta -catenin protein and inappropriate activation of this pathway.

30 The ability to manipulate the genomes of model organisms such as *Drosophila* provides a powerful means to analyze biochemical processes that, due to significant evolutionary conservation, have direct relevance to more complex vertebrate organisms. Due to a high level of gene and pathway conservation, the strong similarity of cellular processes, and the functional conservation of genes between these model organisms and mammals, identification of the involvement of novel genes in particular pathways and their functions in such model organisms can directly contribute to the understanding of the correlative pathways and methods of modulating them in mammals (see, for example, Mechler BM et al., 1985 EMBO J 4:1551-1557; Gateff E. 1982 Adv. Cancer Res. 37: 33-

74; Watson KL., et al., 1994 J Cell Sci. 18: 19-33; Miklos GL, and Rubin GM. 1996 Cell 86:521-529; Wassarman DA, et al., 1995 Curr Opin Gen Dev 5: 44-50; and Booth DR. 1999 Cancer Metastasis Rev. 18: 261-284). For example, a genetic screen can be carried out in an invertebrate model organism having underexpression (e.g. knockout) or
5 overexpression of a gene (referred to as a “genetic entry point”) that yields a visible phenotype. Additional genes are mutated in a random or targeted manner. When a gene mutation changes the original phenotype caused by the mutation in the genetic entry point, the gene is identified as a “modifier” involved in the same or overlapping pathway as the genetic entry point. When the genetic entry point is an ortholog of a human gene
10 implicated in a disease pathway, such as beta-catenin, modifier genes can be identified that may be attractive candidate targets for novel therapeutics.

All references cited herein, including patents, patent applications, publications, and sequence information in referenced Genbank identifier numbers, are incorporated herein in their entireties.

SUMMARY OF THE INVENTION

We have discovered genes that modify the beta-catenin pathway in *Drosophila*, and identified their human orthologs, hereinafter referred to as modifier of beta catenin (MBCAT). The invention provides methods for utilizing these beta-catenin modifier
20 genes and polypeptides to identify MBCAT-modulating agents that are candidate therapeutic agents that can be used in the treatment of disorders associated with defective or impaired beta-catenin function and/or MBCAT function. Preferred MBCAT-modulating agents specifically bind to MBCAT polypeptides and restore beta-catenin function. Other preferred MBCAT-modulating agents are nucleic acid modulators such as
25 antisense oligomers and RNAi that repress MBCAT gene expression or product activity by, for example, binding to and inhibiting the respective nucleic acid (i.e. DNA or mRNA).

MBCAT modulating agents may be evaluated by any convenient *in vitro* or *in vivo* assay for molecular interaction with an MBCAT polypeptide or nucleic acid. In one
30 embodiment, candidate MBCAT modulating agents are tested with an assay system comprising a MBCAT polypeptide or nucleic acid. Agents that produce a change in the activity of the assay system relative to controls are identified as candidate beta-catenin modulating agents. The assay system may be cell-based or cell-free. MBCAT-modulating agents include MBCAT related proteins (e.g. dominant negative mutants, and

biotherapeutics); MBCAT -specific antibodies; MBCAT -specific antisense oligomers and other nucleic acid modulators; and chemical agents that specifically bind to or interact with MBCAT or compete with MBCAT binding partner (e.g. by binding to an MBCAT binding partner). In one specific embodiment, a small molecule modulator is identified
5 using a binding assay. In specific embodiments, the screening assay system is selected from an apoptosis assay, a cell proliferation assay, an angiogenesis assay, and a hypoxic induction assay.

In another embodiment, candidate beta-catenin pathway modulating agents are further tested using a second assay system that detects changes in the beta-catenin
10 pathway, such as angiogenic, apoptotic, or cell proliferation changes produced by the originally identified candidate agent or an agent derived from the original agent. The second assay system may use cultured cells or non-human animals. In specific embodiments, the secondary assay system uses non-human animals, including animals predetermined to have a disease or disorder implicating the beta-catenin pathway, such as
15 an angiogenic, apoptotic, or cell proliferation disorder (e.g. cancer).

The invention further provides methods for modulating the MBCAT function and/or the beta-catenin pathway in a mammalian cell by contacting the mammalian cell with an agent that specifically binds a MBCAT polypeptide or nucleic acid. The agent may be a small molecule modulator, a nucleic acid modulator, or an antibody and may be
20 administered to a mammalian animal predetermined to have a pathology associated with the beta-catenin pathway.

DETAILED DESCRIPTION OF THE INVENTION

In a screen to identify enhancers and suppressors of the Wg signaling pathway, we
25 generated activated beta -catenin models in *Drosophila* based on human tumor data (Polakis (2000) Genes and Development 14: 1837-1851). We identified modifiers of the Wg pathway and identified their orthologs. Accordingly, vertebrate orthologs of these modifiers, and preferably the human orthologs, MBCAT genes (i.e., nucleic acids and polypeptides) are attractive drug targets for the treatment of pathologies associated with a
30 defective beta-catenin signaling pathway, such as cancer. Table 1 (Example II) lists the modifiers and their orthologs.

In vitro and in vivo methods of assessing MBCAT function are provided herein. Modulation of the MBCAT or their respective binding partners is useful for understanding the association of the beta-catenin pathway and its members in normal and disease

conditions and for developing diagnostics and therapeutic modalities for beta-catenin related pathologies. MBCAT-modulating agents that act by inhibiting or enhancing MBCAT expression, directly or indirectly, for example, by affecting an MBCAT function such as enzymatic (e.g., catalytic) or binding activity, can be identified using methods provided herein. MBCAT modulating agents are useful in diagnosis, therapy and pharmaceutical development.

Nucleic acids and polypeptides of the invention

Sequences related to MBCAT nucleic acids and polypeptides that can be used in the invention are disclosed in Genbank (referenced by Genbank identifier (GI) or RefSeq number), shown in Table 1 and in the appended sequence listing.

The term "MBCAT polypeptide" refers to a full-length MBCAT protein or a functionally active fragment or derivative thereof. A "functionally active" MBCAT fragment or derivative exhibits one or more functional activities associated with a full-length, wild-type MBCAT protein, such as antigenic or immunogenic activity, enzymatic activity, ability to bind natural cellular substrates, etc. The functional activity of MBCAT proteins, derivatives and fragments can be assayed by various methods known to one skilled in the art (Current Protocols in Protein Science (1998) Coligan *et al.*, eds., John Wiley & Sons, Inc., Somerset, New Jersey) and as further discussed below. In one embodiment, a functionally active MBCAT polypeptide is a MBCAT derivative capable of rescuing defective endogenous MBCAT activity, such as in cell based or animal assays; the rescuing derivative may be from the same or a different species. For purposes herein, functionally active fragments also include those fragments that comprise one or more structural domains of an MBCAT, such as a binding domain. Protein domains can be identified using the PFAM program (Bateman A., et al., Nucleic Acids Res, 1999, 27:260-2). Methods for obtaining MBCAT polypeptides are also further described below. In some embodiments, preferred fragments are functionally active, domain-containing fragments comprising at least 25 contiguous amino acids, preferably at least 50, more preferably 75, and most preferably at least 100 contiguous amino acids of an MBCAT. In further preferred embodiments, the fragment comprises the entire functionally active domain.

The term "MBCAT nucleic acid" refers to a DNA or RNA molecule that encodes a MBCAT polypeptide. Preferably, the MBCAT polypeptide or nucleic acid or fragment thereof is from a human, but can also be an ortholog, or derivative thereof with at least

70% sequence identity, preferably at least 80%, more preferably 85%, still more preferably 90%, and most preferably at least 95% sequence identity with human MBCAT. Methods of identifying orthologs are known in the art. Normally, orthologs in different species retain the same function, due to presence of one or more protein motifs and/or 3-dimensional structures. Orthologs are generally identified by sequence homology analysis, such as BLAST analysis, usually using protein bait sequences. Sequences are assigned as a potential ortholog if the best hit sequence from the forward BLAST result retrieves the original query sequence in the reverse BLAST (Huynen MA and Bork P, Proc Natl Acad Sci (1998) 95:5849-5856; Huynen MA *et al.*, Genome Research (2000) 10:1204-1210). Programs for multiple sequence alignment, such as CLUSTAL (Thompson JD et al, 1994, Nucleic Acids Res 22:4673-4680) may be used to highlight conserved regions and/or residues of orthologous proteins and to generate phylogenetic trees. In a phylogenetic tree representing multiple homologous sequences from diverse species (e.g., retrieved through BLAST analysis), orthologous sequences from two species generally appear closest on the tree with respect to all other sequences from these two species. Structural threading or other analysis of protein folding (e.g., using software by ProCeryon, Biosciences, Salzburg, Austria) may also identify potential orthologs. In evolution, when a gene duplication event follows speciation, a single gene in one species, such as *Drosophila*, may correspond to multiple genes (paralogs) in another, such as human. As used herein, the term "orthologs" encompasses paralogs. As used herein, "percent (%) sequence identity" with respect to a subject sequence, or a specified portion of a subject sequence, is defined as the percentage of nucleotides or amino acids in the candidate derivative sequence identical with the nucleotides or amino acids in the subject sequence (or specified portion thereof), after aligning the sequences and introducing gaps, if necessary to achieve the maximum percent sequence identity, as generated by the program WU-BLAST-2.0a19 (Altschul *et al.*, J. Mol. Biol. (1997) 215:403-410) with all the search parameters set to default values. The HSP S and HSP S2 parameters are dynamic values and are established by the program itself depending upon the composition of the particular sequence and composition of the particular database against which the sequence of interest is being searched. A % identity value is determined by the number of matching identical nucleotides or amino acids divided by the sequence length for which the percent identity is being reported. "Percent (%) amino acid sequence similarity" is determined by doing the same calculation as for determining % amino acid sequence

identity, but including conservative amino acid substitutions in addition to identical amino acids in the computation.

A conservative amino acid substitution is one in which an amino acid is substituted for another amino acid having similar properties such that the folding or activity of the protein is not significantly affected. Aromatic amino acids that can be substituted for each other are phenylalanine, tryptophan, and tyrosine; interchangeable hydrophobic amino acids are leucine, isoleucine, methionine, and valine; interchangeable polar amino acids are glutamine and asparagine; interchangeable basic amino acids are arginine, lysine and histidine; interchangeable acidic amino acids are aspartic acid and glutamic acid; and interchangeable small amino acids are alanine, serine, threonine, cysteine and glycine.

Alternatively, an alignment for nucleic acid sequences is provided by the local homology algorithm of Smith and Waterman (Smith and Waterman, 1981, *Advances in Applied Mathematics* 2:482-489; database: European Bioinformatics Institute; Smith and Waterman, 1981, *J. of Molec.Biol.*, 147:195-197; Nicholas et al., 1998, "A Tutorial on Searching Sequence Databases and Sequence Scoring Methods" (www.psc.edu) and references cited therein.; W.R. Pearson, 1991, *Genomics* 11:635-650). This algorithm can be applied to amino acid sequences by using the scoring matrix developed by Dayhoff (Dayhoff: *Atlas of Protein Sequences and Structure*, M. O. Dayhoff ed., 5 suppl. 3:353-358, National Biomedical Research Foundation, Washington, D.C., USA), and normalized by Gribskov (Gribskov 1986 *Nucl. Acids Res.* 14(6):6745-6763). The Smith-Waterman algorithm may be employed where default parameters are used for scoring (for example, gap open penalty of 12, gap extension penalty of two). From the data generated, the "Match" value reflects "sequence identity."

Derivative nucleic acid molecules of the subject nucleic acid molecules include sequences that hybridize to the nucleic acid sequence of an MBCAT. The stringency of hybridization can be controlled by temperature, ionic strength, pH, and the presence of denaturing agents such as formamide during hybridization and washing. Conditions routinely used are set out in readily available procedure texts (*e.g.*, *Current Protocol in Molecular Biology*, Vol. 1, Chap. 2.10, John Wiley & Sons, Publishers (1994); Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). In some embodiments, a nucleic acid molecule of the invention is capable of hybridizing to a nucleic acid molecule containing the nucleotide sequence of an MBCAT under high stringency hybridization conditions that are: prehybridization of filters containing nucleic acid for 8 hours to overnight at 65° C in a solution comprising 6X single strength citrate (SSC) (1X SSC is

0.15 M NaCl, 0.015 M Na citrate; pH 7.0), 5X Denhardt's solution, 0.05% sodium pyrophosphate and 100 μ g/ml herring sperm DNA; hybridization for 18-20 hours at 65° C in a solution containing 6X SSC, 1X Denhardt's solution, 100 μ g/ml yeast tRNA and 0.05% sodium pyrophosphate; and washing of filters at 65° C for 1h in a solution
5 containing 0.1X SSC and 0.1% SDS (sodium dodecyl sulfate).

In other embodiments, moderately stringent hybridization conditions are used that are: pretreatment of filters containing nucleic acid for 6 h at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.1% PVP, 0.1% Ficoll, 1% BSA, and 500 μ g/ml denatured salmon sperm DNA; hybridization for 18-20h
10 at 40° C in a solution containing 35% formamide, 5X SSC, 50 mM Tris-HCl (pH7.5), 5mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 μ g/ml salmon sperm DNA, and 10% (wt/vol) dextran sulfate; followed by washing twice for 1 hour at 55° C in a solution containing 2X SSC and 0.1% SDS.

Alternatively, low stringency conditions can be used that are: incubation for 8
15 hours to overnight at 37° C in a solution comprising 20% formamide, 5 x SSC, 50 mM sodium phosphate (pH 7.6), 5X Denhardt's solution, 10% dextran sulfate, and 20 μ g/ml denatured sheared salmon sperm DNA; hybridization in the same buffer for 18 to 20 hours; and washing of filters in 1 x SSC at about 37° C for 1 hour.

20 **Isolation, Production, Expression, and Mis-expression of MBCAT Nucleic Acids and Polypeptides**

MBCAT nucleic acids and polypeptides are useful for identifying and testing agents that modulate MBCAT function and for other applications related to the involvement of MBCAT in the beta-catenin pathway. MBCAT nucleic acids and
25 derivatives and orthologs thereof may be obtained using any available method. For instance, techniques for isolating cDNA or genomic DNA sequences of interest by screening DNA libraries or by using polymerase chain reaction (PCR) are well known in the art. In general, the particular use for the protein will dictate the particulars of expression, production, and purification methods. For instance, production of proteins for
30 use in screening for modulating agents may require methods that preserve specific biological activities of these proteins, whereas production of proteins for antibody generation may require structural integrity of particular epitopes. Expression of proteins to be purified for screening or antibody production may require the addition of specific tags (*e.g.*, generation of fusion proteins). Overexpression of an MBCAT protein for assays

used to assess MBCAT function, such as involvement in cell cycle regulation or hypoxic response, may require expression in eukaryotic cell lines capable of these cellular activities. Techniques for the expression, production, and purification of proteins are well known in the art; any suitable means therefore may be used (e.g., Higgins SJ and Hames BD (eds.) Protein Expression: A Practical Approach, Oxford University Press Inc., New York 1999; Stanbury PF et al., Principles of Fermentation Technology, 2nd edition, Elsevier Science, New York, 1995; Doonan S (ed.) Protein Purification Protocols, Humana Press, New Jersey, 1996; Coligan JE et al, Current Protocols in Protein Science (eds.), 1999, John Wiley & Sons, New York). In particular embodiments, recombinant MBCAT is expressed in a cell line known to have defective beta-catenin function. The recombinant cells are used in cell-based screening assay systems of the invention, as described further below.

The nucleotide sequence encoding an MBCAT polypeptide can be inserted into any appropriate expression vector. The necessary transcriptional and translational signals, including promoter/enhancer element, can derive from the native MBCAT gene and/or its flanking regions or can be heterologous. A variety of host-vector expression systems may be utilized, such as mammalian cell systems infected with virus (e.g. vaccinia virus, adenovirus, *etc.*); insect cell systems infected with virus (e.g. baculovirus); microorganisms such as yeast containing yeast vectors, or bacteria transformed with bacteriophage, plasmid, or cosmid DNA. An isolated host cell strain that modulates the expression of, modifies, and/or specifically processes the gene product may be used.

To detect expression of the MBCAT gene product, the expression vector can comprise a promoter operably linked to an MBCAT gene nucleic acid, one or more origins of replication, and, one or more selectable markers (e.g. thymidine kinase activity, resistance to antibiotics, *etc.*). Alternatively, recombinant expression vectors can be identified by assaying for the expression of the MBCAT gene product based on the physical or functional properties of the MBCAT protein in *in vitro* assay systems (e.g. immunoassays).

The MBCAT protein, fragment, or derivative may be optionally expressed as a fusion, or chimeric protein product (i.e. it is joined via a peptide bond to a heterologous protein sequence of a different protein), for example to facilitate purification or detection. A chimeric product can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acid sequences to each other using standard methods and expressing the chimeric product. A chimeric product may also be made by protein

synthetic techniques, *e.g.* by use of a peptide synthesizer (Hunkapiller *et al.*, Nature (1984) 310:105-111).

Once a recombinant cell that expresses the MBCAT gene sequence is identified, the gene product can be isolated and purified using standard methods (*e.g.* ion exchange, affinity, and gel exclusion chromatography; centrifugation; differential solubility; electrophoresis). Alternatively, native MBCAT proteins can be purified from natural sources, by standard methods (*e.g.* immunoaffinity purification). Once a protein is obtained, it may be quantified and its activity measured by appropriate methods, such as immunoassay, bioassay, or other measurements of physical properties, such as crystallography.

The methods of this invention may also use cells that have been engineered for altered expression (mis-expression) of MBCAT or other genes associated with the beta-catenin pathway. As used herein, mis-expression encompasses ectopic expression, over-expression, under-expression, and non-expression (*e.g.* by gene knock-out or blocking expression that would otherwise normally occur).

Genetically modified animals

Animal models that have been genetically modified to alter MBCAT expression may be used in *in vivo* assays to test for activity of a candidate beta-catenin modulating agent, or to further assess the role of MBCAT in a beta-catenin pathway process such as apoptosis or cell proliferation. Preferably, the altered MBCAT expression results in a detectable phenotype, such as decreased or increased levels of cell proliferation, angiogenesis, or apoptosis compared to control animals having normal MBCAT expression. The genetically modified animal may additionally have altered beta-catenin expression (*e.g.* beta-catenin knockout). Preferred genetically modified animals are mammals such as primates, rodents (preferably mice or rats), among others. Preferred non-mammalian species include zebrafish, *C. elegans*, and *Drosophila*. Preferred genetically modified animals are transgenic animals having a heterologous nucleic acid sequence present as an extrachromosomal element in a portion of its cells, *i.e.* mosaic animals (see, for example, techniques described by Jakobovits, 1994, Curr. Biol. 4:761-763.) or stably integrated into its germ line DNA (*i.e.*, in the genomic sequence of most or all of its cells). Heterologous nucleic acid is introduced into the germ line of such transgenic animals by genetic manipulation of, for example, embryos or embryonic stem cells of the host animal.

Methods of making transgenic animals are well-known in the art (for transgenic mice see Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442 (1985), U.S. Pat. Nos. 4,736,866 and 4,870,009, both by Leder et al., U.S. Pat. No. 4,873,191 by Wagner et al., and Hogan, B., Manipulating the Mouse Embryo, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986); for particle bombardment see U.S. Pat. No., 4,945,050, by Sandford *et al.*; for transgenic *Drosophila* see Rubin and Spradling, Science (1982) 218:348-53 and U.S. Pat. No. 4,670,388; for transgenic insects see Berghammer A.J. *et al.*, A Universal Marker for Transgenic Insects (1999) Nature 402:370-371; for transgenic Zebrafish see Lin S., Transgenic Zebrafish, Methods Mol Biol. (2000);136:375-3830); for microinjection procedures for fish, amphibian eggs and birds see Houdebine and Chourrout, Experientia (1991) 47:897-905; for transgenic rats see Hammer *et al.*, Cell (1990) 63:1099-1112; and for culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection see, e.g., Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E. J. Robertson, ed., IRL Press (1987)). Clones of the nonhuman transgenic animals can be produced according to available methods (see Wilmut, I. *et al.* (1997) Nature 385:810-813; and PCT International Publication Nos. WO 97/07668 and WO 97/07669).

In one embodiment, the transgenic animal is a “knock-out” animal having a heterozygous or homozygous alteration in the sequence of an endogenous MBCAT gene that results in a decrease of MBCAT function, preferably such that MBCAT expression is undetectable or insignificant. Knock-out animals are typically generated by homologous recombination with a vector comprising a transgene having at least a portion of the gene to be knocked out. Typically a deletion, addition or substitution has been introduced into the transgene to functionally disrupt it. The transgene can be a human gene (e.g., from a human genomic clone) but more preferably is an ortholog of the human gene derived from the transgenic host species. For example, a mouse MBCAT gene is used to construct a homologous recombination vector suitable for altering an endogenous MBCAT gene in the mouse genome. Detailed methodologies for homologous recombination in mice are available (see Capecchi, Science (1989) 244:1288-1292; Joyner *et al.*, Nature (1989) 338:153-156). Procedures for the production of non-rodent transgenic mammals and other animals are also available (Houdebine and Chourrout, *supra*; Pursel *et al.*, Science (1989) 244:1281-1288; Simms *et al.*, Bio/Technology (1988) 6:179-183). In a preferred embodiment, knock-out animals, such as mice harboring a knockout of a specific gene,

may be used to produce antibodies against the human counterpart of the gene that has been knocked out (Claesson MH et al., (1994) Scan J Immunol 40:257-264; Declerck PJ et al., (1995) J Biol Chem. 270:8397-400).

In another embodiment, the transgenic animal is a "knock-in" animal having an alteration in its genome that results in altered expression (e.g., increased (including ectopic) or decreased expression) of the MBCAT gene, e.g., by introduction of additional copies of MBCAT, or by operatively inserting a regulatory sequence that provides for altered expression of an endogenous copy of the MBCAT gene. Such regulatory sequences include inducible, tissue-specific, and constitutive promoters and enhancer elements. The knock-in can be homozygous or heterozygous.

Transgenic nonhuman animals can also be produced that contain selected systems allowing for regulated expression of the transgene. One example of such a system that may be produced is the cre/loxP recombinase system of bacteriophage P1 (Lakso *et al.*, PNAS (1992) 89:6232-6236; U.S. Pat. No. 4,959,317). If a cre/loxP recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the Cre recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman et al. (1991) Science 251:1351-1355; U.S. Pat. No. 5,654,182). In a preferred embodiment, both Cre-LoxP and Flp-Frt are used in the same system to regulate expression of the transgene, and for sequential deletion of vector sequences in the same cell (Sun X et al (2000) Nat Genet 25:83-6).

The genetically modified animals can be used in genetic studies to further elucidate the beta-catenin pathway, as animal models of disease and disorders implicating defective beta-catenin function, and for *in vivo* testing of candidate therapeutic agents, such as those identified in screens described below. The candidate therapeutic agents are administered to a genetically modified animal having altered MBCAT function and phenotypic changes are compared with appropriate control animals such as genetically modified animals that receive placebo treatment, and/or animals with unaltered MBCAT expression that receive candidate therapeutic agent.

In addition to the above-described genetically modified animals having altered MBCAT function, animal models having defective beta-catenin function (and otherwise

normal MBCAT function), can be used in the methods of the present invention. For example, a beta-catenin knockout mouse can be used to assess, *in vivo*, the activity of a candidate beta-catenin modulating agent identified in one of the *in vitro* assays described below. Preferably, the candidate beta-catenin modulating agent when administered to a
5 model system with cells defective in beta-catenin function, produces a detectable phenotypic change in the model system indicating that the beta-catenin function is restored, i.e., the cells exhibit normal cell cycle progression.

Modulating Agents

10 The invention provides methods to identify agents that interact with and/or modulate the function of MBCAT and/or the beta-catenin pathway. Modulating agents identified by the methods are also part of the invention. Such agents are useful in a variety of diagnostic and therapeutic applications associated with the beta-catenin pathway, as well as in further analysis of the MBCAT protein and its contribution to the beta-catenin
15 pathway. Accordingly, the invention also provides methods for modulating the beta-catenin pathway comprising the step of specifically modulating MBCAT activity by administering a MBCAT-interacting or -modulating agent.

As used herein, an "MBCAT-modulating agent" is any agent that modulates MBCAT function, for example, an agent that interacts with MBCAT to inhibit or enhance
20 MBCAT activity or otherwise affect normal MBCAT function. MBCAT function can be affected at any level, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In a preferred embodiment, the MBCAT - modulating agent specifically modulates the function of the MBCAT. The phrases "specific modulating agent", "specifically modulates", etc., are used herein to refer to modulating
25 agents that directly bind to the MBCAT polypeptide or nucleic acid, and preferably inhibit, enhance, or otherwise alter, the function of the MBCAT. These phrases also encompass modulating agents that alter the interaction of the MBCAT with a binding partner, substrate, or cofactor (e.g. by binding to a binding partner of an MBCAT, or to a protein/binding partner complex, and altering MBCAT function). In a further preferred
30 embodiment, the MBCAT- modulating agent is a modulator of the beta-catenin pathway (e.g. it restores and/or upregulates beta-catenin function) and thus is also a beta-catenin-modulating agent.

Preferred MBCAT-modulating agents include small molecule compounds; MBCAT-interacting proteins, including antibodies and other biotherapeutics; and nucleic

acid modulators such as antisense and RNA inhibitors. The modulating agents may be formulated in pharmaceutical compositions, for example, as compositions that may comprise other active ingredients, as in combination therapy, and/or suitable carriers or excipients. Techniques for formulation and administration of the compounds may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton, PA, 19th edition.

Small molecule modulators

Small molecules are often preferred to modulate function of proteins with enzymatic function, and/or containing protein interaction domains. Chemical agents, referred to in the art as "small molecule" compounds are typically organic, non-peptide molecules, having a molecular weight up to 10,000, preferably up to 5,000, more preferably up to 1,000, and most preferably up to 500 daltons. This class of modulators includes chemically synthesized molecules, for instance, compounds from combinatorial chemical libraries. Synthetic compounds may be rationally designed or identified based on known or inferred properties of the MBCAT protein or may be identified by screening compound libraries. Alternative appropriate modulators of this class are natural products, particularly secondary metabolites from organisms such as plants or fungi, which can also be identified by screening compound libraries for MBCAT-modulating activity. Methods for generating and obtaining compounds are well known in the art (Schreiber SL, Science (2000) 151: 1964-1969; Radmann J and Gunther J, Science (2000) 151:1947-1948).

Small molecule modulators identified from screening assays, as described below, can be used as lead compounds from which candidate clinical compounds may be designed, optimized, and synthesized. Such clinical compounds may have utility in treating pathologies associated with the beta-catenin pathway. The activity of candidate small molecule modulating agents may be improved several-fold through iterative secondary functional validation, as further described below, structure determination, and candidate modulator modification and testing. Additionally, candidate clinical compounds are generated with specific regard to clinical and pharmacological properties. For example, the reagents may be derivatized and re-screened using *in vitro* and *in vivo* assays to optimize activity and minimize toxicity for pharmaceutical development.

Protein Modulators

Specific MBCAT-interacting proteins are useful in a variety of diagnostic and therapeutic applications related to the beta-catenin pathway and related disorders, as well as in validation assays for other MBCAT-modulating agents. In a preferred embodiment, MBCAT-interacting proteins affect normal MBCAT function, including transcription, protein expression, protein localization, and cellular or extra-cellular activity. In another embodiment, MBCAT-interacting proteins are useful in detecting and providing information about the function of MBCAT proteins, as is relevant to beta-catenin related disorders, such as cancer (e.g., for diagnostic means).

An MBCAT-interacting protein may be endogenous, i.e. one that naturally interacts genetically or biochemically with an MBCAT, such as a member of the MBCAT pathway that modulates MBCAT expression, localization, and/or activity. MBCAT-modulators include dominant negative forms of MBCAT-interacting proteins and of MBCAT proteins themselves. Yeast two-hybrid and variant screens offer preferred methods for identifying endogenous MBCAT-interacting proteins (Finley, R. L. et al. (1996) in DNA Cloning-Expression Systems: A Practical Approach, eds. Glover D. & Hames B. D (Oxford University Press, Oxford, England), pp. 169-203; Fashema SF et al., Gene (2000) 250:1-14; Drees BL Curr Opin Chem Biol (1999) 3:64-70; Vidal M and Legrain P Nucleic Acids Res (1999) 27:919-29; and U.S. Pat. No. 5,928,868). Mass spectrometry is an alternative preferred method for the elucidation of protein complexes (reviewed in, e.g., Pandley A and Mann M, Nature (2000) 405:837-846; Yates JR 3rd, Trends Genet (2000) 16:5-8).

An MBCAT-interacting protein may be an exogenous protein, such as an MBCAT-specific antibody or a T-cell antigen receptor (see, e.g., Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory; Harlow and Lane (1999) Using antibodies: a laboratory manual. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press). MBCAT antibodies are further discussed below.

In preferred embodiments, an MBCAT-interacting protein specifically binds an MBCAT protein. In alternative preferred embodiments, an MBCAT-modulating agent binds an MBCAT substrate, binding partner, or cofactor.

Antibodies

In another embodiment, the protein modulator is an MBCAT specific antibody agonist or antagonist. The antibodies have therapeutic and diagnostic utilities, and can be

used in screening assays to identify MBCAT modulators. The antibodies can also be used in dissecting the portions of the MBCAT pathway responsible for various cellular responses and in the general processing and maturation of the MBCAT.

Antibodies that specifically bind MBCAT polypeptides can be generated using known methods. Preferably the antibody is specific to a mammalian ortholog of MBCAT polypeptide, and more preferably, to human MBCAT. Antibodies may be polyclonal, monoclonal (mAbs), humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab')₂ fragments, fragments produced by a FAb expression library, anti-idiotypic (anti-Id) antibodies, and epitope-binding fragments of any of the above.

Epitopes of MBCAT which are particularly antigenic can be selected, for example, by routine screening of MBCAT polypeptides for antigenicity or by applying a theoretical method for selecting antigenic regions of a protein (Hopp and Wood (1981), Proc. Natl. Acad. Sci. U.S.A. 78:3824-28; Hopp and Wood, (1983) Mol. Immunol. 20:483-89; Sutcliffe et al., (1983) Science 219:660-66) to the amino acid sequence of an MBCAT.

Monoclonal antibodies with affinities of 10^8 M^{-1} preferably 10^9 M^{-1} to 10^{10} M^{-1} , or stronger can be made by standard procedures as described (Harlow and Lane, *supra*; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York; and U.S. Pat. Nos. 4,381,292; 4,451,570; and 4,618,577). Antibodies may be generated against crude cell extracts of MBCAT or substantially purified fragments thereof. If MBCAT fragments are used, they preferably comprise at least 10, and more preferably, at least 20 contiguous amino acids of an MBCAT protein. In a particular embodiment, MBCAT-specific antigens and/or immunogens are coupled to carrier proteins that stimulate the immune response. For example, the subject polypeptides are covalently coupled to the keyhole limpet hemocyanin (KLH) carrier, and the conjugate is emulsified in Freund's complete adjuvant, which enhances the immune response. An appropriate immune system such as a laboratory rabbit or mouse is immunized according to conventional protocols.

The presence of MBCAT-specific antibodies is assayed by an appropriate assay such as a solid phase enzyme-linked immunosorbant assay (ELISA) using immobilized corresponding MBCAT polypeptides. Other assays, such as radioimmunoassays or fluorescent assays might also be used.

Chimeric antibodies specific to MBCAT polypeptides can be made that contain different portions from different animal species. For instance, a human immunoglobulin constant region may be linked to a variable region of a murine mAb, such that the

antibody derives its biological activity from the human antibody, and its binding specificity from the murine fragment. Chimeric antibodies are produced by splicing together genes that encode the appropriate regions from each species (Morrison et al., Proc. Natl. Acad. Sci. (1984) 81:6851-6855; Neuberger et al., Nature (1984) 312:604-608;

5 Takeda et al., Nature (1985) 31:452-454). Humanized antibodies, which are a form of chimeric antibodies, can be generated by grafting complementary-determining regions (CDRs) (Carlos, T. M., J. M. Harlan. 1994. Blood 84:2068-2101) of mouse antibodies into a background of human framework regions and constant regions by recombinant DNA technology (Riechmann LM, et al., 1988 Nature 323: 323-327). Humanized
10 antibodies contain ~10% murine sequences and ~90% human sequences, and thus further reduce or eliminate immunogenicity, while retaining the antibody specificities (Co MS, and Queen C. 1991 Nature 351: 501-501; Morrison SL. 1992 Ann. Rev. Immun. 10:239-265). Humanized antibodies and methods of their production are well-known in the art (U.S. Pat. Nos. 5,530,101, 5,585,089, 5,693,762, and 6,180,370).

15 MBCAT-specific single chain antibodies which are recombinant, single chain polypeptides formed by linking the heavy and light chain fragments of the Fv regions via an amino acid bridge, can be produced by methods known in the art (U.S. Pat. No. 4,946,778; Bird, Science (1988) 242:423-426; Huston et al., Proc. Natl. Acad. Sci. USA (1988) 85:5879-5883; and Ward et al., Nature (1989) 334:544-546).

20 Other suitable techniques for antibody production involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors (Huse et al., Science (1989) 246:1275-1281). As used herein, T-cell antigen receptors are included within the scope of antibody modulators (Harlow and Lane, 1988, *supra*).

25 The polypeptides and antibodies of the present invention may be used with or without modification. Frequently, antibodies will be labeled by joining, either covalently or non-covalently, a substance that provides for a detectable signal, or that is toxic to cells that express the targeted protein (Menard S, et al., Int J. Biol Markers (1989) 4:131-134). A wide variety of labels and conjugation techniques are known and are reported
30 extensively in both the scientific and patent literature. Suitable labels include radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, fluorescent emitting lanthanide metals, chemiluminescent moieties, bioluminescent moieties, magnetic particles, and the like (U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241). Also, recombinant immunoglobulins

may be produced (U.S. Pat. No. 4,816,567). Antibodies to cytoplasmic polypeptides may be delivered and reach their targets by conjugation with membrane-penetrating toxin proteins (U.S. Pat. No. 6,086,900).

When used therapeutically in a patient, the antibodies of the subject invention are typically administered parenterally, when possible at the target site, or intravenously. The therapeutically effective dose and dosage regimen is determined by clinical studies. Typically, the amount of antibody administered is in the range of about 0.1 mg/kg –to about 10 mg/kg of patient weight. For parenteral administration, the antibodies are formulated in a unit dosage injectable form (e.g., solution, suspension, emulsion) in association with a pharmaceutically acceptable vehicle. Such vehicles are inherently nontoxic and non-therapeutic. Examples are water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Nonaqueous vehicles such as fixed oils, ethyl oleate, or liposome carriers may also be used. The vehicle may contain minor amounts of additives, such as buffers and preservatives, which enhance isotonicity and chemical stability or otherwise enhance therapeutic potential. The antibodies' concentrations in such vehicles are typically in the range of about 1 mg/ml to about 10 mg/ml. Immunotherapeutic methods are further described in the literature (US Pat. No. 5,859,206; WO0073469).

Specific biotherapeutics

In a preferred embodiment, an MBCAT-interacting protein may have biotherapeutic applications. Biotherapeutic agents formulated in pharmaceutically acceptable carriers and dosages may be used to activate or inhibit signal transduction pathways. This modulation may be accomplished by binding a ligand, thus inhibiting the activity of the pathway; or by binding a receptor, either to inhibit activation of, or to activate, the receptor. Alternatively, the biotherapeutic may itself be a ligand capable of activating or inhibiting a receptor. Biotherapeutic agents and methods of producing them are described in detail in U.S. Pat. No. 6,146,628.

When the MBCAT is a ligand, it may be used as a biotherapeutic agent to activate or inhibit its natural receptor. Alternatively, antibodies against MBCAT, as described in the previous section, may be used as biotherapeutic agents.

When the MBCAT is a receptor, its ligand(s), antibodies to the ligand(s) or the MBCAT itself may be used as biotherapeutics to modulate the activity of MBCAT in the beta-catenin pathway.

Nucleic Acid Modulators

Other preferred MBCAT-modulating agents comprise nucleic acid molecules, such as antisense oligomers or double stranded RNA (dsRNA), which generally inhibit MBCAT activity. Preferred nucleic acid modulators interfere with the function of the MBCAT nucleic acid such as DNA replication, transcription, translocation of the MBCAT RNA to the site of protein translation, translation of protein from the MBCAT RNA, splicing of the MBCAT RNA to yield one or more mRNA species, or catalytic activity which may be engaged in or facilitated by the MBCAT RNA.

In one embodiment, the antisense oligomer is an oligonucleotide that is sufficiently complementary to an MBCAT mRNA to bind to and prevent translation, preferably by binding to the 5' untranslated region. MBCAT-specific antisense oligonucleotides, preferably range from at least 6 to about 200 nucleotides. In some embodiments the oligonucleotide is preferably at least 10, 15, or 20 nucleotides in length. In other embodiments, the oligonucleotide is preferably less than 50, 40, or 30 nucleotides in length. The oligonucleotide can be DNA or RNA or a chimeric mixture or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents that facilitate transport across the cell membrane, hybridization-triggered cleavage agents, and intercalating agents.

In another embodiment, the antisense oligomer is a phosphothioate morpholino oligomer (PMO). PMOs are assembled from four different morpholino subunits, each of which contain one of four genetic bases (A, C, G, or T) linked to a six-membered morpholine ring. Polymers of these subunits are joined by non-ionic phosphoramidate intersubunit linkages. Details of how to make and use PMOs and other antisense oligomers are well known in the art (e.g. see WO99/18193; Probst JC, Antisense Oligodeoxynucleotide and Ribozyme Design, Methods. (2000) 22(3):271-281; Summerton J, and Weller D. 1997 Antisense Nucleic Acid Drug Dev. :7:187-95; US Pat. No. 5,235,033; and US Pat No. 5,378,841).

Alternative preferred MBCAT nucleic acid modulators are double-stranded RNA species mediating RNA interference (RNAi). RNAi is the process of sequence-specific, post-transcriptional gene silencing in animals and plants, initiated by double-stranded RNA (dsRNA) that is homologous in sequence to the silenced gene. Methods relating to the use of RNAi to silence genes in *C. elegans*, *Drosophila*, plants, and humans are known

in the art (Fire A, et al., 1998 Nature 391:806-811; Fire, A. Trends Genet. 15, 358-363 (1999); Sharp, P. A. RNA interference 2001. Genes Dev. 15, 485-490 (2001); Hammond, S. M., et al., Nature Rev. Genet. 2, 110-1119 (2001); Tuschl, T. Chem. Biochem. 2, 239-245 (2001); Hamilton, A. et al., Science 286, 950-952 (1999); Hammond, S. M., et al.,
5 Nature 404, 293-296 (2000); Zamore, P. D., et al., Cell 101, 25-33 (2000); Bernstein, E., et al., Nature 409, 363-366 (2001); Elbashir, S. M., et al., Genes Dev. 15, 188-200 (2001); WO0129058; WO9932619; Elbashir SM, et al., 2001 Nature 411:494-498).

Nucleic acid modulators are commonly used as research reagents, diagnostics, and therapeutics. For example, antisense oligonucleotides, which are able to inhibit gene
10 expression with exquisite specificity, are often used to elucidate the function of particular genes (see, for example, U.S. Pat. No. 6,165,790). Nucleic acid modulators are also used, for example, to distinguish between functions of various members of a biological pathway. For example, antisense oligomers have been employed as therapeutic moieties in the treatment of disease states in animals and man and have been demonstrated in numerous
15 clinical trials to be safe and effective (Milligan JF, *et al*, Current Concepts in Antisense Drug Design, J Med Chem. (1993) 36:1923-1937; Tonkinson JL *et al.*, Antisense Oligodeoxynucleotides as Clinical Therapeutic Agents, Cancer Invest. (1996) 14:54-65). Accordingly, in one aspect of the invention, an MBCAT-specific nucleic acid modulator is used in an assay to further elucidate the role of the MBCAT in the beta-catenin pathway,
20 and/or its relationship to other members of the pathway. In another aspect of the invention, an MBCAT-specific antisense oligomer is used as a therapeutic agent for treatment of beta-catenin-related disease states.

Assay Systems

25 The invention provides assay systems and screening methods for identifying specific modulators of MBCAT activity. As used herein, an "assay system" encompasses all the components required for performing and analyzing results of an assay that detects and/or measures a particular event. In general, primary assays are used to identify or confirm a modulator's specific biochemical or molecular effect with respect to the
30 MBCAT nucleic acid or protein. In general, secondary assays further assess the activity of a MBCAT modulating agent identified by a primary assay and may confirm that the modulating agent affects MBCAT in a manner relevant to the beta-catenin pathway. In some cases, MBCAT modulators will be directly tested in a secondary assay.

In a preferred embodiment, the screening method comprises contacting a suitable assay system comprising an MBCAT polypeptide or nucleic acid with a candidate agent under conditions whereby, but for the presence of the agent, the system provides a reference activity (e.g. binding activity), which is based on the particular molecular event the screening method detects. A statistically significant difference between the agent-biased activity and the reference activity indicates that the candidate agent modulates MBCAT activity, and hence the beta-catenin pathway. The MBCAT polypeptide or nucleic acid used in the assay may comprise any of the nucleic acids or polypeptides described above.

Primary Assays

The type of modulator tested generally determines the type of primary assay.

Primary assays for small molecule modulators

For small molecule modulators, screening assays are used to identify candidate modulators. Screening assays may be cell-based or may use a cell-free system that recreates or retains the relevant biochemical reaction of the target protein (reviewed in Sittampalam GS *et al.*, Curr Opin Chem Biol (1997) 1:384-91 and accompanying references). As used herein the term "cell-based" refers to assays using live cells, dead cells, or a particular cellular fraction, such as a membrane, endoplasmic reticulum, or mitochondrial fraction. The term "cell free" encompasses assays using substantially purified protein (either endogenous or recombinantly produced), partially purified or crude cellular extracts. Screening assays may detect a variety of molecular events, including protein-DNA interactions, protein-protein interactions (*e.g.*, receptor-ligand binding), transcriptional activity (*e.g.*, using a reporter gene), enzymatic activity (*e.g.*, via a property of the substrate), activity of second messengers, immunogenicity and changes in cellular morphology or other cellular characteristics. Appropriate screening assays may use a wide range of detection methods including fluorescent, radioactive, colorimetric, spectrophotometric, and amperometric methods, to provide a read-out for the particular molecular event detected.

Cell-based screening assays usually require systems for recombinant expression of MBCAT and any auxiliary proteins demanded by the particular assay. Appropriate methods for generating recombinant proteins produce sufficient quantities of proteins that retain their relevant biological activities and are of sufficient purity to optimize activity

and assure assay reproducibility. Yeast two-hybrid and variant screens, and mass spectrometry provide preferred methods for determining protein-protein interactions and elucidation of protein complexes. In certain applications, when MBCAT-interacting proteins are used in screens to identify small molecule modulators, the binding specificity of the interacting protein to the MBCAT protein may be assayed by various known methods such as substrate processing (e.g. ability of the candidate MBCAT-specific binding agents to function as negative effectors in MBCAT-expressing cells), binding equilibrium constants (usually at least about 10^7 M^{-1} , preferably at least about 10^8 M^{-1} , more preferably at least about 10^9 M^{-1}), and immunogenicity (e.g. ability to elicit MBCAT specific antibody in a heterologous host such as a mouse, rat, goat or rabbit). For enzymes and receptors, binding may be assayed by, respectively, substrate and ligand processing.

The screening assay may measure a candidate agent's ability to specifically bind to or modulate activity of a MBCAT polypeptide, a fusion protein thereof, or to cells or membranes bearing the polypeptide or fusion protein. The MBCAT polypeptide can be full length or a fragment thereof that retains functional MBCAT activity. The MBCAT polypeptide may be fused to another polypeptide, such as a peptide tag for detection or anchoring, or to another tag. The MBCAT polypeptide is preferably human MBCAT, or is an ortholog or derivative thereof as described above. In a preferred embodiment, the screening assay detects candidate agent-based modulation of MBCAT interaction with a binding target, such as an endogenous or exogenous protein or other substrate that has MBCAT-specific binding activity, and can be used to assess normal MBCAT gene function.

Suitable assay formats that may be adapted to screen for MBCAT modulators are known in the art. Preferred screening assays are high throughput or ultra high throughput and thus provide automated, cost-effective means of screening compound libraries for lead compounds (Fernandes PB, *Curr Opin Chem Biol* (1998) 2:597-603; Sundberg SA, *Curr Opin Biotechnol* 2000, 11:47-53). In one preferred embodiment, screening assays uses fluorescence technologies, including fluorescence polarization, time-resolved fluorescence, and fluorescence resonance energy transfer. These systems offer means to monitor protein-protein or DNA-protein interactions in which the intensity of the signal emitted from dye-labeled molecules depends upon their interactions with partner molecules (e.g., Selvin PR, *Nat Struct Biol* (2000) 7:730-4; Fernandes PB, *supra*; Hertzberg RP and Pope AJ, *Curr Opin Chem Biol* (2000) 4:445-451).

A variety of suitable assay systems may be used to identify candidate MBCAT and beta-catenin pathway modulators (e.g. U.S. Pat. Nos. 5,550,019 and 6,133,437 (apoptosis assays); WO 01/25487 (Helicase assays), U.S. Pat. No. 6,114,132 (phosphatase and protease assays), U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434 (angiogenesis assays), among others). Specific preferred assays are described in more detail below.

Protein phosphatases catalyze the removal of a gamma phosphate from a serine, threonine or tyrosine residue in a protein substrate. Since phosphatases act in opposition to kinases, appropriate assays measure the same parameters as kinase assays. In one example, the dephosphorylation of a fluorescently labeled peptide substrate allows trypsin cleavage of the substrate, which in turn renders the cleaved substrate significantly more fluorescent (Nishikata M *et al.*, Biochem J (1999) 343:35-391). In another example, fluorescence polarization (FP), a solution-based, homogeneous technique requiring no immobilization or separation of reaction components, is used to develop high throughput screening (HTS) assays for protein phosphatases. This assay uses direct binding of the phosphatase with the target, and increasing concentrations of target- phosphatase increase the rate of dephosphorylation, leading to a change in polarization (Parker GJ *et al.*, (2000) J Biomol Screen 5:77-88).

Proteases are enzymes that cleave protein substrates at specific sites. Exemplary assays detect the alterations in the spectral properties of an artificial substrate that occur upon protease-mediated cleavage. In one example, synthetic caspase substrates containing four amino acid proteolysis recognition sequences, separating two different fluorescent tags are employed; fluorescence resonance energy transfer detects the proximity of these fluorophores, which indicates whether the substrate is cleaved (Mahajan NP *et al.*, Chem Biol (1999) 6:401-409).

Polymerases catalyze the extension of newly synthesized DNA or RNA chains. Their activity may be monitored in an assay that uses labeled nucleotide analogs. For instance, a colorimetric polymerase assay monitors RNA synthesis using labeled ATP and GTP (Vassiliou W *et al.*, Virology (2000) 274:429-437).

Apoptosis assays. Assays for apoptosis may be performed by terminal deoxynucleotidyl transferase-mediated digoxigenin-11-dUTP nick end labeling (TUNEL) assay. The TUNEL assay is used to measure nuclear DNA fragmentation characteristic of apoptosis (Lazebnik *et al.*, 1994, Nature 371, 346), by following the incorporation of fluorescein-dUTP (Yonehara *et al.*, 1989, J. Exp. Med. 169, 1747). Apoptosis may further

be assayed by acridine orange staining of tissue culture cells (Lucas, R., et al., 1998, Blood 15:4730-41). Other cell-based apoptosis assays include the caspase-3/7 assay and the cell death nucleosome ELISA assay. The caspase 3/7 assay is based on the activation of the caspase cleavage activity as part of a cascade of events that occur during programmed cell death in many apoptotic pathways. In the caspase 3/7 assay (commercially available Apo-ONE™ Homogeneous Caspase-3/7 assay from Promega, cat# 67790), lysis buffer and caspase substrate are mixed and added to cells. The caspase substrate becomes fluorescent when cleaved by active caspase 3/7. The nucleosome ELISA assay is a general cell death assay known to those skilled in the art, and available commercially (Roche, Cat# 1774425). This assay is a quantitative sandwich-enzyme-immunoassay which uses monoclonal antibodies directed against DNA and histones respectively, thus specifically determining amount of mono- and oligonucleosomes in the cytoplasmic fraction of cell lysates. Mono and oligonucleosomes are enriched in the cytoplasm during apoptosis due to the fact that DNA fragmentation occurs several hours before the plasma membrane breaks down, allowing for accumulation in the cytoplasm. Nucleosomes are not present in the cytoplasmic fraction of cells that are not undergoing apoptosis. An apoptosis assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the apoptosis assay system and changes in induction of apoptosis relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, an apoptosis assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using a cell-free assay system. An apoptosis assay may also be used to test whether MBCAT function plays a direct role in apoptosis. For example, an apoptosis assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in apoptotic response compared to wild type cells suggests that the MBCAT plays a direct role in the apoptotic response. Apoptosis assays are described further in US Pat. No. 6,133,437.

Cell proliferation and cell cycle assays. Cell proliferation may be assayed via bromodeoxyuridine (BRDU) incorporation. This assay identifies a cell population undergoing DNA synthesis by incorporation of BRDU into newly-synthesized DNA. Newly-synthesized DNA may then be detected using an anti-BRDU antibody (Hoshino *et*

al., 1986, *Int. J. Cancer* 38, 369; Campana *et al.*, 1988, *J. Immunol. Meth.* 107, 79), or by other means.

Cell proliferation is also assayed via phospho-histone H3 staining, which identifies a cell population undergoing mitosis by phosphorylation of histone H3. Phosphorylation of histone H3 at serine 10 is detected using an antibody specific to the phosphorylated form of the serine 10 residue of histone H3. (Chadlee, D.N. 1995, *J. Biol. Chem* 270:20098-105). Cell Proliferation may also be examined using [³H]-thymidine incorporation (Chen, J., 1996, *Oncogene* 13:1395-403; Jeoung, J., 1995, *J. Biol. Chem.* 270:18367-73). This assay allows for quantitative characterization of S-phase DNA syntheses. In this assay, cells synthesizing DNA will incorporate [³H]-thymidine into newly synthesized DNA. Incorporation can then be measured by standard techniques such as by counting of radioisotope in a scintillation counter (e.g., Beckman LS 3800 Liquid Scintillation Counter). Another proliferation assay uses the dye Alamar Blue (available from Biosource International), which fluoresces when reduced in living cells and provides an indirect measurement of cell number (Voytik-Harbin SL *et al.*, 1998, *In Vitro Cell Dev Biol Anim* 34:239-46). Yet another proliferation assay, the MTS assay, is based on in vitro cytotoxicity assessment of industrial chemicals, and uses the soluble tetrazolium salt, MTS. MTS assays are commercially available, for example, the Promega CellTiter 96[®] Aqueous Non-Radioactive Cell Proliferation Assay (Cat.# G5421).

Cell proliferation may also be assayed by colony formation in soft agar (Sambrook *et al.*, *Molecular Cloning*, Cold Spring Harbor (1989)). For example, cells transformed with MBCAT are seeded in soft agar plates, and colonies are measured and counted after two weeks incubation.

Cell proliferation may also be assayed by measuring ATP levels as indicator of metabolically active cells. Such assays are commercially available, for example Cell Titer-Glo[™], which is a luminescent homogeneous assay available from Promega.

Involvement of a gene in the cell cycle may be assayed by flow cytometry (Gray JW *et al.* (1986) *Int J Radiat Biol Relat Stud Phys Chem Med* 49:237-55). Cells transfected with an MBCAT may be stained with propidium iodide and evaluated in a flow cytometer (available from Becton Dickinson), which indicates accumulation of cells in different stages of the cell cycle.

Accordingly, a cell proliferation or cell cycle assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent

can be added to the assay system and changes in cell proliferation or cell cycle relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the cell proliferation or cell cycle assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system such as a cell-free assay system. A cell proliferation assay may also be used to test whether MBCAT function plays a direct role in cell proliferation or cell cycle. For example, a cell proliferation or cell cycle assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in proliferation or cell cycle compared to wild type cells suggests that the MBCAT plays a direct role in cell proliferation or cell cycle.

Angiogenesis. Angiogenesis may be assayed using various human endothelial cell systems, such as umbilical vein, coronary artery, or dermal cells. Suitable assays include Alamar Blue based assays (available from Biosource International) to measure proliferation; migration assays using fluorescent molecules, such as the use of Becton Dickinson Falcon HTS FluoroBlock cell culture inserts to measure migration of cells through membranes in presence or absence of angiogenesis enhancer or suppressors; and tubule formation assays based on the formation of tubular structures by endothelial cells on Matrigel® (Becton Dickinson). Accordingly, an angiogenesis assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the angiogenesis assay system and changes in angiogenesis relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the angiogenesis assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system. An angiogenesis assay may also be used to test whether MBCAT function plays a direct role in cell proliferation. For example, an angiogenesis assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in angiogenesis compared to wild type cells suggests that the MBCAT plays a direct role in angiogenesis. U.S. Pat. Nos. 5,976,782, 6,225,118 and 6,444,434, among others, describe various angiogenesis assays.

Hypoxic induction. The alpha subunit of the transcription factor, hypoxia inducible factor-1 (HIF-1), is upregulated in tumor cells following exposure to hypoxia in

vitro. Under hypoxic conditions, HIF-1 stimulates the expression of genes known to be important in tumour cell survival, such as those encoding glycolytic enzymes and VEGF. Induction of such genes by hypoxic conditions may be assayed by growing cells transfected with MBCAT in hypoxic conditions (such as with 0.1% O₂, 5% CO₂, and balance N₂, generated in a Napco 7001 incubator (Precision Scientific)) and normoxic conditions, followed by assessment of gene activity or expression by Taqman®. For example, a hypoxic induction assay system may comprise a cell that expresses an MBCAT, and that optionally has defective beta-catenin function (e.g. beta-catenin is over-expressed or under-expressed relative to wild-type cells). A test agent can be added to the hypoxic induction assay system and changes in hypoxic response relative to controls where no test agent is added, identify candidate beta-catenin modulating agents. In some embodiments of the invention, the hypoxic induction assay may be used as a secondary assay to test a candidate beta-catenin modulating agents that is initially identified using another assay system. A hypoxic induction assay may also be used to test whether MBCAT function plays a direct role in the hypoxic response. For example, a hypoxic induction assay may be performed on cells that over- or under-express MBCAT relative to wild type cells. Differences in hypoxic response compared to wild type cells suggests that the MBCAT plays a direct role in hypoxic induction.

Cell adhesion. Cell adhesion assays measure adhesion of cells to purified adhesion proteins, or adhesion of cells to each other, in presence or absence of candidate modulating agents. Cell-protein adhesion assays measure the ability of agents to modulate the adhesion of cells to purified proteins. For example, recombinant proteins are produced, diluted to 2.5g/mL in PBS, and used to coat the wells of a microtiter plate. The wells used for negative control are not coated. Coated wells are then washed, blocked with 1% BSA, and washed again. Compounds are diluted to 2× final test concentration and added to the blocked, coated wells. Cells are then added to the wells, and the unbound cells are washed off. Retained cells are labeled directly on the plate by adding a membrane-permeable fluorescent dye, such as calcein-AM, and the signal is quantified in a fluorescent microplate reader.

Cell-cell adhesion assays measure the ability of agents to modulate binding of cell adhesion proteins with their native ligands. These assays use cells that naturally or recombinantly express the adhesion protein of choice. In an exemplary assay, cells expressing the cell adhesion protein are plated in wells of a multiwell plate. Cells

expressing the ligand are labeled with a membrane-permeable fluorescent dye, such as BCECF, and allowed to adhere to the monolayers in the presence of candidate agents. Unbound cells are washed off, and bound cells are detected using a fluorescence plate reader.

5 High-throughput cell adhesion assays have also been described. In one such assay, small molecule ligands and peptides are bound to the surface of microscope slides using a microarray spotter, intact cells are then contacted with the slides, and unbound cells are washed off. In this assay, not only the binding specificity of the peptides and modulators against cell lines are determined, but also the functional cell signaling of attached cells
10 using immunofluorescence techniques in situ on the microchip is measured (Falsey JR et al., Bioconjug Chem. 2001 May-Jun;12(3):346-53).

Tubulogenesis. Tubulogenesis assays monitor the ability of cultured cells, generally endothelial cells, to form tubular structures on a matrix substrate, which
15 generally simulates the environment of the extracellular matrix. Exemplary substrates include MatrigelTM (Becton Dickinson), an extract of basement membrane proteins containing laminin, collagen IV, and heparin sulfate proteoglycan, which is liquid at 4° C and forms a solid gel at 37° C. Other suitable matrices comprise extracellular components such as collagen, fibronectin, and/or fibrin. Cells are stimulated with a pro-angiogenic
20 stimulant, and their ability to form tubules is detected by imaging. Tubules can generally be detected after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Tube formation assays are well known in the art (e.g., Jones MK et al., 1999, Nature Medicine 5:1418-1423). These assays have traditionally involved stimulation with serum or with the growth factors FGF or VEGF. Serum represents an
25 undefined source of growth factors. In a preferred embodiment, the assay is performed with cells cultured in serum free medium, in order to control which process or pathway a candidate agent modulates. Moreover, we have found that different target genes respond differently to stimulation with different pro-angiogenic agents, including inflammatory angiogenic factors such as TNF- α . Thus, in a further preferred embodiment, a
30 tubulogenesis assay system comprises testing an MBCAT's response to a variety of factors, such as FGF, VEGF, phorbol myristate acetate (PMA), TNF- α , ephrin, etc.

Cell Migration. An invasion/migration assay (also called a migration assay) tests the ability of cells to overcome a physical barrier and to migrate towards pro-angiogenic

signals. Migration assays are known in the art (e.g., Paik JH et al., 2001, J Biol Chem 276:11830-11837). In a typical experimental set-up, cultured endothelial cells are seeded onto a matrix-coated porous lamina, with pore sizes generally smaller than typical cell size. The matrix generally simulates the environment of the extracellular matrix, as described above. The lamina is typically a membrane, such as the transwell polycarbonate membrane (Corning Costar Corporation, Cambridge, MA), and is generally part of an upper chamber that is in fluid contact with a lower chamber containing pro-angiogenic stimuli. Migration is generally assayed after an overnight incubation with stimuli, but longer or shorter time frames may also be used. Migration is assessed as the number of cells that crossed the lamina, and may be detected by staining cells with hemotoxylin solution (VWR Scientific, South San Francisco, CA), or by any other method for determining cell number. In another exemplary set up, cells are fluorescently labeled and migration is detected using fluorescent readings, for instance using the Falcon HTS FluoroBlok (Becton Dickinson). While some migration is observed in the absence of stimulus, migration is greatly increased in response to pro-angiogenic factors. As described above, a preferred assay system for migration/invasion assays comprises testing an MBCAT's response to a variety of pro-angiogenic factors, including tumor angiogenic and inflammatory angiogenic agents, and culturing the cells in serum free medium.

Sprouting assay. A sprouting assay is a three-dimensional *in vitro* angiogenesis assay that uses a cell-number defined spheroid aggregation of endothelial cells ("spheroid"), embedded in a collagen gel-based matrix. The spheroid can serve as a starting point for the sprouting of capillary-like structures by invasion into the extracellular matrix (termed "cell sprouting") and the subsequent formation of complex anastomosing networks (Korff and Augustin, 1999, J Cell Sci 112:3249-58). In an exemplary experimental set-up, spheroids are prepared by pipetting 400 human umbilical vein endothelial cells into individual wells of a nonadhesive 96-well plates to allow overnight spheroidal aggregation (Korff and Augustin: J Cell Biol 143: 1341-52, 1998). Spheroids are harvested and seeded in 900 μ l of methocel-collagen solution and pipetted into individual wells of a 24 well plate to allow collagen gel polymerization. Test agents are added after 30 min by pipetting 100 μ l of 10-fold concentrated working dilution of the test substances on top of the gel. Plates are incubated at 37°C for 24h. Dishes are fixed at the end of the experimental incubation period by addition of paraformaldehyde. Sprouting

intensity of endothelial cells can be quantitated by an automated image analysis system to determine the cumulative sprout length per spheroid.

Primary assays for antibody modulators

5 For antibody modulators, appropriate primary assays test is a binding assay that tests the antibody's affinity to and specificity for the MBCAT protein. Methods for testing antibody affinity and specificity are well known in the art (Harlow and Lane, 1988, 1999, *supra*). The enzyme-linked immunosorbant assay (ELISA) is a preferred method for detecting MBCAT-specific antibodies; others include FACS assays, radioimmunoassays, and fluorescent assays.

10 In some cases, screening assays described for small molecule modulators may also be used to test antibody modulators.

Primary assays for nucleic acid modulators

15 For nucleic acid modulators, primary assays may test the ability of the nucleic acid modulator to inhibit or enhance MBCAT gene expression, preferably mRNA expression. In general, expression analysis comprises comparing MBCAT expression in like populations of cells (*e.g.*, two pools of cells that endogenously or recombinantly express MBCAT) in the presence and absence of the nucleic acid modulator. Methods for analyzing mRNA and protein expression are well known in the art. For instance, Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR (*e.g.*, using the TaqMan®, PE Applied Biosystems), or microarray analysis may be used to confirm that MBCAT mRNA expression is reduced in cells treated with the nucleic acid modulator (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm DH and Guiseppi-Elie, A Curr Opin Biotechnol 2001, 12:41-47). Protein expression may also be monitored. Proteins are most commonly detected with specific antibodies or antisera directed against either the MBCAT protein or specific peptides. A variety of means including Western blotting, ELISA, or in situ detection, are available (Harlow E and Lane D, 1988 and 1999, *supra*).

25 In some cases, screening assays described for small molecule modulators, particularly in assay systems that involve MBCAT mRNA expression, may also be used to test nucleic acid modulators.

Secondary Assays

Secondary assays may be used to further assess the activity of MBCAT-modulating agent identified by any of the above methods to confirm that the modulating agent affects MBCAT in a manner relevant to the beta-catenin pathway. As used herein, MBCAT-modulating agents encompass candidate clinical compounds or other agents derived from previously identified modulating agent. Secondary assays can also be used to test the activity of a modulating agent on a particular genetic or biochemical pathway or to test the specificity of the modulating agent's interaction with MBCAT.

Secondary assays generally compare like populations of cells or animals (*e.g.*, two pools of cells or animals that endogenously or recombinantly express MBCAT) in the presence and absence of the candidate modulator. In general, such assays test whether treatment of cells or animals with a candidate MBCAT-modulating agent results in changes in the beta-catenin pathway in comparison to untreated (or mock- or placebo-treated) cells or animals. Certain assays use “sensitized genetic backgrounds”, which, as used herein, describe cells or animals engineered for altered expression of genes in the beta-catenin or interacting pathways.

Cell-based assays

Cell based assays may detect endogenous beta-catenin pathway activity or may rely on recombinant expression of beta-catenin pathway components. Any of the aforementioned assays may be used in this cell-based format. Candidate modulators are typically added to the cell media but may also be injected into cells or delivered by any other efficacious means.

Animal Assays

A variety of non-human animal models of normal or defective beta-catenin pathway may be used to test candidate MBCAT modulators. Models for defective beta-catenin pathway typically use genetically modified animals that have been engineered to mis-express (*e.g.*, over-express or lack expression in) genes involved in the beta-catenin pathway. Assays generally require systemic delivery of the candidate modulators, such as by oral administration, injection, etc.

In a preferred embodiment, beta-catenin pathway activity is assessed by monitoring neovascularization and angiogenesis. Animal models with defective and normal beta-catenin are used to test the candidate modulator's affect on MBCAT in

Matrigel® assays. Matrigel® is an extract of basement membrane proteins, and is composed primarily of laminin, collagen IV, and heparin sulfate proteoglycan. It is provided as a sterile liquid at 4° C, but rapidly forms a solid gel at 37° C. Liquid Matrigel® is mixed with various angiogenic agents, such as bFGF and VEGF, or with human tumor cells which over-express the MBCAT. The mixture is then injected subcutaneously(SC) into female athymic nude mice (Taconic, Germantown, NY) to support an intense vascular response. Mice with Matrigel® pellets may be dosed via oral (PO), intraperitoneal (IP), or intravenous (IV) routes with the candidate modulator. Mice are euthanized 5 - 12 days post-injection, and the Matrigel® pellet is harvested for hemoglobin analysis (Sigma plasma hemoglobin kit). Hemoglobin content of the gel is found to correlate the degree of neovascularization in the gel.

In another preferred embodiment, the effect of the candidate modulator on MBCAT is assessed via tumorigenicity assays. Tumor xenograft assays are known in the art (see, e.g., Ogawa K et al., 2000, *Oncogene* 19:6043-6052). Xenografts are typically implanted SC into female athymic mice, 6-7 week old, as single cell suspensions either from a pre-existing tumor or from *in vitro* culture. The tumors which express the MBCAT endogenously are injected in the flank, 1×10^5 to 1×10^7 cells per mouse in a volume of 100 μ L using a 27gauge needle. Mice are then ear tagged and tumors are measured twice weekly. Candidate modulator treatment is initiated on the day the mean tumor weight reaches 100 mg. Candidate modulator is delivered IV, SC, IP, or PO by bolus administration. Depending upon the pharmacokinetics of each unique candidate modulator, dosing can be performed multiple times per day. The tumor weight is assessed by measuring perpendicular diameters with a caliper and calculated by multiplying the measurements of diameters in two dimensions. At the end of the experiment, the excised tumors maybe utilized for biomarker identification or further analyses. For immunohistochemistry staining, xenograft tumors are fixed in 4% paraformaldehyde, 0.1M phosphate, pH 7.2, for 6 hours at 4°C, immersed in 30% sucrose in PBS, and rapidly frozen in isopentane cooled with liquid nitrogen.

In another preferred embodiment, tumorigenicity is monitored using a hollow fiber assay, which is described in U.S. Pat No. US 5,698,413. Briefly, the method comprises implanting into a laboratory animal a biocompatible, semi-permeable encapsulation device containing target cells, treating the laboratory animal with a candidate modulating agent, and evaluating the target cells for reaction to the candidate modulator. Implanted cells are generally human cells from a pre-existing tumor or a tumor cell line. After an appropriate

period of time, generally around six days, the implanted samples are harvested for evaluation of the candidate modulator. Tumorogenicity and modulator efficacy may be evaluated by assaying the quantity of viable cells present in the macrocapsule, which can be determined by tests known in the art, for example, MTT dye conversion assay, neutral red dye uptake, trypan blue staining, viable cell counts, the number of colonies formed in soft agar, the capacity of the cells to recover and replicate in vitro, etc.

In another preferred embodiment, a tumorogenicity assay use a transgenic animal, usually a mouse, carrying a dominant oncogene or tumor suppressor gene knockout under the control of tissue specific regulatory sequences; these assays are generally referred to as transgenic tumor assays. In a preferred application, tumor development in the transgenic model is well characterized or is controlled. In an exemplary model, the "RIP1-Tag2" transgene, comprising the SV40 large T-antigen oncogene under control of the insulin gene regulatory regions is expressed in pancreatic beta cells and results in islet cell carcinomas (Hanahan D, 1985, Nature 315:115-122; Parangi S et al, 1996, Proc Natl Acad Sci USA 93: 2002-2007; Bergers G et al, 1999, Science 284:808-812). An "angiogenic switch," occurs at approximately five weeks, as normally quiescent capillaries in a subset of hyperproliferative islets become angiogenic. The RIP1-TAG2 mice die by age 14 weeks. Candidate modulators may be administered at a variety of stages, including just prior to the angiogenic switch (e.g., for a model of tumor prevention), during the growth of small tumors (e.g., for a model of intervention), or during the growth of large and/or invasive tumors (e.g., for a model of regression). Tumorogenicity and modulator efficacy can be evaluating life-span extension and/or tumor characteristics, including number of tumors, tumor size, tumor morphology, vessel density, apoptotic index, etc.

Diagnostic and therapeutic uses

Specific MBCAT-modulating agents are useful in a variety of diagnostic and therapeutic applications where disease or disease prognosis is related to defects in the beta-catenin pathway, such as angiogenic, apoptotic, or cell proliferation disorders. Accordingly, the invention also provides methods for modulating the beta-catenin pathway in a cell, preferably a cell pre-determined to have defective or impaired beta-catenin function (e.g. due to overexpression, underexpression, or misexpression of beta-catenin, or due to gene mutations), comprising the step of administering an agent to the cell that specifically modulates MBCAT activity. Preferably, the modulating agent produces a detectable phenotypic change in the cell indicating that the beta-catenin function is

restored. The phrase “function is restored”, and equivalents, as used herein, means that the desired phenotype is achieved, or is brought closer to normal compared to untreated cells. For example, with restored beta-catenin function, cell proliferation and/or progression through cell cycle may normalize, or be brought closer to normal relative to untreated cells. The invention also provides methods for treating disorders or disease associated with impaired beta-catenin function by administering a therapeutically effective amount of an MBCAT -modulating agent that modulates the beta-catenin pathway. The invention further provides methods for modulating MBCAT function in a cell, preferably a cell pre-determined to have defective or impaired MBCAT function, by administering an MBCAT -modulating agent. Additionally, the invention provides a method for treating disorders or disease associated with impaired MBCAT function by administering a therapeutically effective amount of an MBCAT -modulating agent.

The discovery that MBCAT is implicated in beta-catenin pathway provides for a variety of methods that can be employed for the diagnostic and prognostic evaluation of diseases and disorders involving defects in the beta-catenin pathway and for the identification of subjects having a predisposition to such diseases and disorders.

Various expression analysis methods can be used to diagnose whether MBCAT expression occurs in a particular sample, including Northern blotting, slot blotting, ribonuclease protection, quantitative RT-PCR, and microarray analysis. (*e.g.*, Current Protocols in Molecular Biology (1994) Ausubel FM *et al.*, eds., John Wiley & Sons, Inc., chapter 4; Freeman WM *et al.*, Biotechniques (1999) 26:112-125; Kallioniemi OP, Ann Med 2001, 33:142-147; Blohm and Guiseppi-Elie, Curr Opin Biotechnol 2001, 12:41-47). Tissues having a disease or disorder implicating defective beta-catenin signaling that express an MBCAT, are identified as amenable to treatment with an MBCAT modulating agent. In a preferred application, the beta-catenin defective tissue overexpresses an MBCAT relative to normal tissue. For example, a Northern blot analysis of mRNA from tumor and normal cell lines, or from tumor and matching normal tissue samples from the same patient, using full or partial MBCAT cDNA sequences as probes, can determine whether particular tumors express or overexpress MBCAT. Alternatively, the TaqMan® is used for quantitative RT-PCR analysis of MBCAT expression in cell lines, normal tissues and tumor samples (PE Applied Biosystems).

Various other diagnostic methods may be performed, for example, utilizing reagents such as the MBCAT oligonucleotides, and antibodies directed against an MBCAT, as described above for: (1) the detection of the presence of MBCAT gene

mutations, or the detection of either over- or under-expression of MBCAT mRNA relative to the non-disorder state; (2) the detection of either an over- or an under-abundance of MBCAT gene product relative to the non-disorder state; and (3) the detection of perturbations or abnormalities in the signal transduction pathway mediated by MBCAT.

5 Kits for detecting expression of MBCAT in various samples, comprising at least one antibody specific to MBCAT, all reagents and/or devices suitable for the detection of antibodies, the immobilization of antibodies, and the like, and instructions for using such kits in diagnosis or therapy are also provided.

Thus, in a specific embodiment, the invention is drawn to a method for diagnosing
10 a disease or disorder in a patient that is associated with alterations in MBCAT expression, the method comprising: a) obtaining a biological sample from the patient; b) contacting the sample with a probe for MBCAT expression; c) comparing results from step (b) with a control; and d) determining whether step (c) indicates a likelihood of the disease or disorder. Preferably, the disease is cancer. The probe may be either DNA or protein,
15 including an antibody.

EXAMPLES

The following experimental section and examples are offered by way of illustration and not by way of limitation.

I. Drosophila beta-catenin screen

Two dominant loss of function screens were carried out in *Drosophila* to identify genes that interact with the Wg cell signaling molecule, beta -catenin (Riggelman et al. (1990) Cell 63:549-560; Peifer et al. (1991) Development 111:1029-1043). Late stage
25 activation of the pathway in the developing *Drosophila* eye leads to apoptosis (Freeman and Bienz (2001) EMBO reports 2: 157-162), whereas early stage activation leads to an overgrowth phenotype. We discovered that ectopic expression of the activated protein in the wing results in changes of cell fate into ectopic bristles and wing veins.

Each transgene was carried in a separate fly stock:

30 Stocks and genotypes were as follows:

eye overgrowth transgene: isow; P{3.5 eyeless-Gal4}; P{arm(S56F)-pExp-UAS}}/TM6b;

eye apoptosis transgene: y w; P{arm(S56F)-pExp-GMR}/CyO; and

wing transgene: P{arm(Δ N)-pExp-VgMQ}/FM7c

In the first dominant loss of function screen, females of each of these three transgenes were crossed to a collection of males containing genomic deficiencies. Resulting progeny containing the transgene and the deficiency were then scored for the effect of the deficiency on the eye apoptosis, eye overgrowth, and wing phenotypes, i.e., whether the deficiency enhanced, suppressed, or had no effect on their respective phenotypes. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifying deficiencies of the phenotypes were then prioritized according to how they modified each of the three phenotypes.

Transposons contained within the prioritized deficiencies were then screened as described. Females of each of the three transgenes were crossed to a collection of 4 types of transposons (3 piggyBac-based and 1 P-element-based). The resulting progeny containing the transgene and the transposon were scored for the effect of the transposon on their respective phenotypes. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifiers of the phenotypes were identified as either members of the Wg pathway, components of apoptotic related pathways, components of cell cycle related pathways, or cell adhesion related proteins.

In the second dominant loss of function screen, females of the eye overgrowth transgene were crossed to males from a collection of 3 types of piggyBac-based transposons. The resulting progeny containing the transgene and the transposon were scored for the effect of the transposon on the eye overgrowth phenotype. All data was recorded and all modifiers were retested with a repeat of the original cross. Modifiers of the phenotypes were identified as either members of the Wg pathway, components of cell cycle related pathways, or cell adhesion related proteins.

II. Analysis of Table 1

BLAST analysis (Altschul et al., *supra*) was employed to identify orthologs of *Drosophila* modifiers. The columns "MBCAT symbol", and "MBCAT name aliases" provide a symbol and the known name abbreviations for the Targets, where available, from Genbank. "MBCAT RefSeq_NA or GI_NA", "MBCAT GI_AA", "MBCAT NAME", and "MBCAT Description" provide the reference DNA sequences for the MBCATs as available from National Center for Biology Information (NCBI), MBCAT protein Genbank identifier number (GI#), MBCAT name, and MBCAT description, all available from Genbank, respectively. The length of each amino acid is in the "MBCAT Protein Length" column.

Names and Protein sequences of *Drosophila* modifiers of beta-catenin from screen (Example I), are represented in the "Modifier Name" and "Modifier GI_AA" column by GI#, respectively.

5 Table 1

MBCAT symbol	MBCAT name aliases	MBCAT RefSeq_NA or GI_NA	NA SEQ ID NO:	MBCAT GI_AA or RefSeq_A A	AA SEQ ID NO:	MBCAT name	MBCAT description	MBCAT protein length	Modifier name	Modifier GI_AA
POLR2E	POLR2E RPB5 XAP4 RPABC1 hRPB25 hsRPB5 DNA directed RNA polymerase II 23 kda polypeptide polymerase (RNA) II (DNA directed) polypeptide E (25kD) polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	NM_002695	1	14589951	28	polymerase (RNA) II (DNA directed) polypeptide E, 25kDa	protein binding; DNA-directed RNA polymerase III; DNA-directed RNA polymerase II; DNA-directed RNA polymerase I	210	Rpb5	17945808
PPP1R3B	PPP1R3B GL PPP1R4 FLJ14005 protein phosphatase 1, regulatory (inhibitor) subunit 3B	NM_024607	2	13375815	29	protein phosphatase 1, regulatory (inhibitor) subunit 3B	protein phosphatase type 1, regulator; enzyme activator; protein binding; protein phosphatase 1 binding; protein phosphatase	285	CG9238	24664201

PPP1R3C	PPP1R3C PPP1R5 Phosphatase 1, regulatory inhibitor subunit 5 protein phosphatase 1, regulatory (inhibitor) subunit 3C	NM_005398	3	4885559	30	protein phosphatase 1, regulatory (inhibitor) subunit 3C	protein phosphatase type 1, regulator; protein phosphatase 1 binding; protein phosphatase type 1	317	CG9238	24664201
LOC135264	LOC135264 similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] na	XM_069258	4	17463746	31	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	118	RpS12	24663646
LOC201829	LOC201829 similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] na	XM_116207	5	20471875	32	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	115	RpS12	24663646
LOC221147	LOC221147 similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] na	XM_169335	6	20548341	33	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	110	RpS12	24663646
LOC253068	LOC253068 similar to 40S ribosomal protein S12 na	XM_171698	7	22055843	34	similar to 40S ribosomal protein S12	na	96	RpS12	24663646

LOC2832 10	LOC2832 10 similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens] na	XM_208564	8	27485488	35	similar to ribosomal protein S12; 40S ribosomal protein S12 [Homo sapiens]	na	132	RpS12	2466364 6
RPS12	RPS12 40S ribosomal protein S12 ribosomal protein S12	NM_001016	9	14277700	36	ribosomal protein S12	RNA binding; structural constituent of ribosome	132	RpS12	2466364 6
C20orf13	C20orf13 FLJ20212 dJ585I14. 2 chromoso me 20 open reading frame 13	NM_017714	10	8923202	37	chromoso me 20 open reading frame 13	asparaginase	420	CG5241	2135789 3
MADH6	MADH6 MADH7 SMAD6 Mothers against decapenta plegic, drosophila , homolog of, 6 MAD (mothers against decapenta plegic, Drosophil a) homolog 6 MAD, mothers against decapenta plegic homolog 6 (Drosophil a)	NM_005585	11	19923323	38	MAD, mothers against decapenta plegic homolog 6 (Drosophil a)	protein binding; protein binding; receptor signaling protein serine/threoni ne kinase signaling protein; signal transducer; TGFbeta receptor, cytoplasmic mediator	496	Dad	1713738 2

MADH7	MADH7 MADH8 SMAD7 Mothers against decapenta plegic, drosophila , homolog of, 7 MAD (mothers against decapenta plegic, Drosophil a) homolog 7 MAD, mothers against decapenta plegic homolog 7 (Drosophil a)	NM_005904	12	5174517	39	MAD, mothers against decapenta plegic homolog 7 (Drosophil a)	apoptosis activator; protein binding; receptor signaling protein serine/threoni ne kinase signaling protein; TGFbeta receptor, inhibitory cytoplasmic mediator; TGFbeta receptor, cytoplasmic mediator; TGFbeta receptor, cytoplasmic mediator	426	Dad	1713738 2
DUSP1	DUSP1 HVH1 CL100 MKP-1 PTPN10 serine/thre onine specific protein phosphata se dual specificity phosphata se 1	NM_004417	13	4758204	40	dual specificity phosphata se 1	protein kinase inhibitor; protein kinase inhibitor; non- membrane spanning protein tyrosine phosphatase; MAP kinase phosphatase; MAP kinase phosphatase	367	Mkp3	1664849 2
DUSP2	DUSP2 PAC1 PAC-1 Dual- specificity phosphata se 2 serine/thre onine specific protein phosphata se dual specificity phosphata se 2	NM_004418	14	4758206	41	dual specificity phosphata se 2	protein tyrosine phosphatase; protein tyrosine/threo nine phosphatase	314	Mkp3	1664849 2

DUSP5	DUSP5 HVH3 VH1-like phosphatase 3 serine/threonine specific protein phosphatase dual specificity phosphatase 5	NM_004419	15	12707566	42	dual specificity phosphatase 5	protein tyrosine phosphatase; MAP kinase phosphatase	384	Mkp3	1664849 2
DUSP6	DUSP6 MKP3 MKP-3 PYST1 MAP kinase phosphatase 3 serine/threonine specific protein phosphatase dual specificity phosphatase 6	NM_001946 NM_022652	16	4503419	43	dual specificity phosphatase 6	protein phosphatase; protein phosphatase; protein tyrosine/threonine phosphatase; MAP kinase phosphatase	381	Mkp3	1664849 2
DUSP7	DUSP7 MKPX MKP-X PYST2 Dual- specificity phosphatase-7 dual specificity phosphatase 7	XM_037430	17	27481087	44	dual specificity phosphatase 7	protein binding; protein phosphatase; JUN kinase phosphatase; MAP kinase phosphatase	419	Mkp3	1664849 2
DUSP8	DUSP8 HB5 HVH8 HVH-5 H1 phosphatase, vaccinia virus homolog serine/threonine specific protein phosphatase dual specificity phosphatase	NM_004420	18	4758212	45	dual specificity phosphatase 8	protein tyrosine phosphatase	625	Mkp3	1664849 2

	se 8									
DUSP9	DUSP9 MKP4 MKP-4 map kinase phosphata se 4 serine/thre onine specific protein phosphata se dual specificity phosphata se 9	NM_001395	19	4503421	46	dual specificity phosphata se 9	protein kinase inhibitor; protein phosphatase	384	Mkp3	1664849 2
DUSP4	DUSP4 1 TYP HvH2 MKP2 MKP-2 MAP kinase phosphata se 2 VH1 homologo us phosphata se 2 serine/thre onine specific protein phosphata se dual specificity phosphata se 4	NM_001394 NM_05715 8	20	6808068	47	dual specificity phosphata se 4	protein binding; protein serine/threoni ne phosphatase; protein serine/threoni ne phosphatase; protein tyrosine/threo nine phosphatase	303	Mkp3	1664849 2
LOC8369 3	LOC8369 3 steroid dehydroge nase-like	NM_031463	21	24432037	48	steroid dehydroge nase-like	metabolism; metabolism; sex determination ; development; development	330	CG31810	2294668 0
7h3	7h3 FLJ13511 hypothetic al protein FLJ13511	NM_033025	22	24432043	49	hypothetic al protein FLJ13511	Rho protein signal transduction	668	RhoGAP1 00F	7302107
MGC3363 7	MGC3363 7 hypothetic al protein MGC3363 7	NM_152596	23	22749225	50	hypothetic al protein MGC3363 7	na	475	egl	2162666 0

SCAP	SCAP KIAA0199 SREBP CLEAVAGE-ACTIVATING PROTEIN	NM_012235	24	30923298	51	SREBP CLEAVAGE-ACTIVATING PROTEIN	na	1278	SCAP	28573975
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III. High-Throughput In Vitro Fluorescence Polarization Assay

Fluorescently-labeled MBCAT peptide/substrate are added to each well of a 96-well microtiter plate, along with a test agent in a test buffer (10 mM HEPES, 10 mM NaCl, 6 mM magnesium chloride, pH 7.6). Changes in fluorescence polarization, determined by using a Fluorolite FPM-2 Fluorescence Polarization Microtiter System (Dynatech Laboratories, Inc), relative to control values indicates the test compound is a candidate modifier of MBCAT activity.

IV. High-Throughput In Vitro Binding Assay.

³³P-labeled MBCAT peptide is added in an assay buffer (100 mM KCl, 20 mM HEPES pH 7.6, 1 mM MgCl₂, 1% glycerol, 0.5% NP-40, 50 mM beta-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors) along with a test agent to the wells of a Neutralite-avidin coated assay plate and incubated at 25°C for 1 hour. Biotinylated substrate is then added to each well and incubated for 1 hour. Reactions are stopped by washing with PBS, and counted in a scintillation counter. Test agents that cause a difference in activity relative to control without test agent are identified as candidate beta-catenin modulating agents.

V. Immunoprecipitations and Immunoblotting

For coprecipitation of transfected proteins, 3×10^6 appropriate recombinant cells containing the MBCAT proteins are plated on 10-cm dishes and transfected on the following day with expression constructs. The total amount of DNA is kept constant in each transfection by adding empty vector. After 24 h, cells are collected, washed once with phosphate-buffered saline and lysed for 20 min on ice in 1 ml of lysis buffer containing 50 mM Hepes, pH 7.9, 250 mM NaCl, 20 mM -glycerophosphate, 1 mM sodium orthovanadate, 5 mM p-nitrophenyl phosphate, 2 mM dithiothreitol, protease inhibitors (complete, Roche Molecular Biochemicals), and 1% Nonidet P-40. Cellular debris is removed by centrifugation twice at $15,000 \times g$ for 15 min. The cell lysate is incubated with 25 μ l of M2 beads (Sigma) for 2 h at 4 °C with gentle rocking.

After extensive washing with lysis buffer, proteins bound to the beads are solubilized by boiling in SDS sample buffer, fractionated by SDS-polyacrylamide gel electrophoresis, transferred to polyvinylidene difluoride membrane and blotted with the indicated antibodies. The reactive bands are visualized with horseradish peroxidase

coupled to the appropriate secondary antibodies and the enhanced chemiluminescence (ECL) Western blotting detection system (Amersham Pharmacia Biotech).

VI. Expression analysis

5 All cell lines used in the following experiments are NCI (National Cancer Institute) lines, and are available from ATCC (American Type Culture Collection, Manassas, VA 20110-2209). Normal and tumor tissues are obtained from Impath, UC Davis, Clontech, Stratagene, Ardaïs, Genome Collaborative, and Ambion.

10 TaqMan® analysis is used to assess expression levels of the disclosed genes in various samples.

RNA is extracted from each tissue sample using Qiagen (Valencia, CA) RNeasy kits, following manufacturer's protocols, to a final concentration of 50ng/μl. Single stranded cDNA is then synthesized by reverse transcribing the RNA samples using random hexamers and 500ng of total RNA per reaction, following protocol 4304965 of 15 Applied Biosystems (Foster City, CA).

Primers for expression analysis using TaqMan® assay (Applied Biosystems, Foster City, CA) are prepared according to the TaqMan® protocols, and the following criteria: a) primer pairs are designed to span introns to eliminate genomic contamination, and b) each primer pair produced only one product. Expression analysis is performed 20 using a 7900HT instrument.

TaqMan® reactions are carried out following manufacturer's protocols, in 25 μl total volume for 96-well plates and 10 μl total volume for 384-well plates, using 300nM primer and 250 nM probe, and approximately 25ng of cDNA. The standard curve for result analysis is prepared using a universal pool of human cDNA samples, which is a 25 mixture of cDNAs from a wide variety of tissues so that the chance that a target will be present in appreciable amounts is good. The raw data are normalized using 18S rRNA (universally expressed in all tissues and cells).

For each expression analysis, tumor tissue samples are compared with matched normal tissues from the same patient. A gene is considered overexpressed in a tumor 30 when the level of expression of the gene is 2 fold or higher in the tumor compared with its matched normal sample. In cases where normal tissue is not available, a universal pool of cDNA samples is used instead. In these cases, a gene is considered overexpressed in a tumor sample when the difference of expression levels between a tumor sample and the average of all normal samples from the same tissue type is greater than 2 times the

standard deviation of all normal samples (i.e., Tumor – average(all normal samples) > 2 x STDEV(all normal samples)).

5 A modulator identified by an assay described herein can be further validated for therapeutic effect by administration to a tumor in which the gene is overexpressed. A decrease in tumor growth confirms therapeutic utility of the modulator. Prior to treating a patient with the modulator, the likelihood that the patient will respond to treatment can be diagnosed by obtaining a tumor sample from the patient, and assaying for expression of the gene targeted by the modulator. The expression data for the gene(s) can also be used as a diagnostic marker for disease progression. The assay can be performed by expression analysis as described above, by antibody directed to the gene target, or by any other
10 available detection method.

WHAT IS CLAIMED IS:

1. A method of identifying a candidate beta-catenin pathway modulating agent, said method comprising the steps of:

- 5 (a) providing an assay system comprising a MBCAT polypeptide or nucleic acid;
 (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity; and
 (c) detecting a test agent-biased activity of the assay system, wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as
10 a candidate beta-catenin pathway modulating agent.

2. The method of Claim 1 wherein the assay system comprises cultured cells that express the MBCAT polypeptide.

- 15 3. The method of Claim 2 wherein the cultured cells additionally have defective beta-catenin function.

4. The method of Claim 1 wherein the assay system includes a screening assay comprising a MBCAT polypeptide, and the candidate test agent is a small molecule
20 modulator.

5. The method of Claim 4 wherein the assay is a binding assay.

6. The method of Claim 1 wherein the assay system is selected from the group consisting
25 of an apoptosis assay system, a cell proliferation assay system, an angiogenesis assay system, and a hypoxic induction assay system.

7. The method of Claim 1 wherein the assay system includes a binding assay comprising a MBCAT polypeptide and the candidate test agent is an antibody.
30

8. The method of Claim 1 wherein the assay system includes an expression assay comprising a MBCAT nucleic acid and the candidate test agent is a nucleic acid modulator.

9. The method of Claim 8 wherein the nucleic acid modulator is an antisense oligomer.

10. The method of Claim 8 wherein the nucleic acid modulator is a PMO.

5 11. The method of Claim 1 additionally comprising:

(d) administering the candidate beta-catenin pathway modulating agent identified in (c) to a model system comprising cells defective in beta-catenin function and, detecting a phenotypic change in the model system that indicates that the beta-catenin function is restored.

10

12. The method of Claim 11 wherein the model system is a mouse model with defective beta-catenin function.

15

13. A method for modulating a beta-catenin pathway of a cell comprising contacting a cell defective in beta-catenin function with a candidate modulator that specifically binds to a MBCAT polypeptide, whereby beta-catenin function is restored.

20

14. The method of Claim 13 wherein the candidate modulator is administered to a vertebrate animal predetermined to have a disease or disorder resulting from a defect in beta-catenin function.

15. The method of Claim 13 wherein the candidate modulator is selected from the group consisting of an antibody and a small molecule.

25

16. The method of Claim 1, comprising the additional steps of:

(e) providing a secondary assay system comprising cultured cells or a non-human animal expressing MBCAT ,

30

(f) contacting the secondary assay system with the test agent of (b) or an agent derived therefrom under conditions whereby, but for the presence of the test agent or agent derived therefrom, the system provides a reference activity; and

(g) detecting an agent-biased activity of the second assay system,

wherein a difference between the agent-biased activity and the reference activity of the second assay system confirms the test agent or agent derived therefrom as a candidate beta-catenin pathway modulating agent,

and wherein the second assay detects an agent-biased change in the beta-catenin pathway.

17. The method of Claim 16 wherein the secondary assay system comprises cultured
5 cells.

18. The method of Claim 16 wherein the secondary assay system comprises a non-human animal.

10 19. The method of Claim 18 wherein the non-human animal mis-expresses a beta-catenin pathway gene.

20. A method of modulating beta-catenin pathway in a mammalian cell comprising
contacting the cell with an agent that specifically binds a MBCAT polypeptide or nucleic
15 acid.

21. The method of Claim 20 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with the beta-catenin pathway.

20 22. The method of Claim 20 wherein the agent is a small molecule modulator, a nucleic acid modulator, or an antibody.

23. A method for diagnosing a disease in a patient comprising:

- (a) obtaining a biological sample from the patient;
- 25 (b) contacting the sample with a probe for MBCAT expression;
- (c) comparing results from step (b) with a control;
- (d) determining whether step (c) indicates a likelihood of disease.

24. The method of Claim 23 wherein said disease is cancer.

30

SEQUENCE LISTING

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<120> MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

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<151> 2003-03-13

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<211> 2262

<212> DNA

<213> Homo sapiens

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 <213> Homo sapiens

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 <213> Homo sapiens

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<210> 28
<211> 210
<212> PRT
<213> Homo sapiens

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<400> 28

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Ile Met Gln Leu Cys His Asp Arg Gly Tyr Leu Val Thr Gln Asp Glu
20          25          30

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Leu Asp Gln Thr Leu Glu Glu Phe Lys Ala Gln Phe Gly Asp Lys Pro
35          40          45

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Ser Glu Gly Arg Pro Arg Arg Thr Asp Leu Thr Val Leu Val Ala His
50          55          60

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Asn Asp Asp Pro Thr Asp Gln Met Phe Val Phe Phe Pro Glu Glu Pro

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130				135				140							
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<210> 29
<211> 285
<212> PRT
<213> Homo sapiens
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<400> 29

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			20					25					30		
Pro	Leu	Arg	Pro	Cys	Ile	Gln	Leu	Ser	Ser	Lys	Asn	Glu	Ala	Ser	Gly
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Phe Ala Asp Asn Gln Gly Leu Ala Leu Thr Met Val Lys Val Phe Ser
65 70 75 80

Glu Phe Asp Asp Pro Leu Asp Met Pro Phe Asn Ile Thr Glu Leu Leu
85 90 95

Asp Asn Ile Val Ser Leu Thr Thr Ala Glu Ser Glu Ser Phe Val Leu
100 105 110

Asp Phe Ser Gln Pro Ser Ala Asp Tyr Leu Asp Phe Arg Asn Arg Leu
115 120 125

Gln Ala Asp His Val Cys Leu Glu Asn Cys Val Leu Lys Asp Lys Ala
130 135 140

Ile Ala Gly Thr Ala Lys Val Gln Asn Leu Ala Phe Glu Lys Thr Val
145 150 155 160

Lys Ile Arg Met Thr Phe Asp Thr Trp Lys Ser Tyr Thr Asp Phe Pro
165 170 175

Cys Gln Tyr Val Lys Asp Thr Tyr Ala Gly Ser Asp Arg Asp Thr Phe
180 185 190

Ser Phe Asp Ile Ser Leu Pro Glu Lys Ile Gln Ser Tyr Glu Arg Met
195 200 205

Glu Phe Ala Val Tyr Tyr Glu Cys Asn Gly Gln Thr Tyr Trp Asp Ser
210 215 220

Asn Arg Gly Lys Asn Tyr Arg Ile Ile Arg Ala Glu Leu Lys Ser Thr
225 230 235 240

Gln Gly Met Thr Lys Pro His Ser Gly Pro Asp Leu Gly Ile Ser Phe
245 250 255

Asp Gln Phe Gly Ser Pro Arg Cys Ser Tyr Gly Leu Phe Pro Glu Trp
260 265 270

Pro Ser Tyr Leu Gly Tyr Glu Lys Leu Gly Pro Tyr Tyr
275 280 285

<210> 30
<211> 317
<212> PRT
<213> Homo sapiens

<400> 30

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 Ser Pro Pro Val Lys Ser Phe Leu Gly Pro Tyr Asp Glu Phe Gln Arg
 35 40 45
 Arg His Phe Val Asn Lys Leu Lys Pro Leu Lys Ser Cys Leu Asn Ile
 50 55 60
 Lys His Lys Ala Lys Ser Gln Asn Asp Trp Lys Cys Ser His Asn Gln
 65 70 75 80
 Ala Lys Lys Arg Val Val Phe Ala Asp Ser Lys Gly Leu Ser Leu Thr
 85 90 95
 Ala Ile His Val Phe Ser Asp Leu Pro Glu Glu Pro Ala Trp Asp Leu
 100 105 110
 Gln Phe Asp Leu Leu Asp Leu Asn Asp Ile Ser Ser Ala Leu Lys His
 115 120 125
 His Glu Glu Lys Asn Leu Ile Leu Asp Phe Pro Gln Pro Ser Thr Asp
 130 135 140
 Tyr Leu Ser Phe Arg Ser His Phe Gln Lys Asn Phe Val Cys Leu Glu
 145 150 155 160
 Asn Cys Ser Leu Gln Glu Arg Thr Val Thr Gly Thr Val Lys Val Lys
 165 170 175
 Asn Val Ser Phe Glu Lys Lys Val Gln Ile Arg Ile Thr Phe Asp Ser
 180 185 190
 Trp Lys Asn Tyr Thr Asp Val Asp Cys Val Tyr Met Lys Asn Val Tyr
 195 200 205
 Gly Gly Thr Asp Ser Asp Thr Phe Ser Phe Ala Ile Asp Leu Pro Pro
 210 215 220
 Val Ile Pro Thr Glu Gln Lys Ile Glu Phe Cys Ile Ser Tyr His Ala
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 Asn Gly Gln Val Phe Trp Asp Asn Asn Asp Gly Gln Asn Tyr Arg Ile

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<400> 32

Met Ala Glu Glu Gly Ile Thr Ala Gly Gly Ile Met Glu Val Asn Thr
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Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Val His Asp Gly Pro Ala
 20 25 30

Cys Gly Ile Leu Glu Ala Ala Lys Ala Leu Asp Lys Cys Gln Ala His
 35 40 45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Val Tyr Val Lys Leu
 50 55 60

Val Glu Ala Phe Cys Ala Glu His Arg Thr Asn Arg Leu Lys Arg Gly
 65 70 75 80

Glu Ser Gly Cys Lys Val Val Gly Gly Ser Cys Val Glu Val Lys Asp
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Ala Gly Lys Glu Cys Gln Ala Lys Asp Val Ile Lys Glu Tyr Phe Lys
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Cys Lys Lys
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<210> 33

<211> 110

<212> PRT

<213> Homo sapiens

<400> 33

Met Ala Lys Glu Gly Ile Ala Ala Gly Gly Val Met Asp Ile Asn Thr
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Ala Leu Gln Glu Val Leu Lys Thr Thr Leu Ile His Asp Gly Leu Ala
 20 25 30

Arg Gly Ile His Glu Ala Ala Lys Pro Leu Asp Lys Gly Gln Ala His
 35 40 45

Leu Tyr Val Leu Ala Ser Asn Cys Asp Glu Thr Val Tyr Val Lys Leu
 50 55 60

Val Glu Ala Ile Cys Ala Lys His Gln Ile Asn Phe Ile Lys Val Asp
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Asp Asn Lys Lys Val Gly Glu Trp Leu Arg Thr Met Ala Arg Asn Leu
 85 90 95

Arg Pro Arg Met Ser Leu Glu Glu Tyr Phe Lys Cys Lys Lys
 100 105 110

<210> 34
 <211> 96
 <212> PRT
 <213> Homo sapiens

<400> 34

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 20 25 30

Arg Gly Ile Arg Glu Ala Ala Lys Ala Leu Asp Lys Cys Trp Ala His
 35 40 45

Pro Cys Ala Ala Pro Asn Ser Cys Leu Cys Gly Trp Leu Val Lys Ala
 50 55 60

Leu Val Ala Glu His Gln Ile Thr Leu Ile Lys Val Asp Asp Asn Lys
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Leu Gly Glu Gly Met Asp His Cys Lys Thr Asp Arg Arg Lys Thr Pro
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<210> 35
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 35

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 20 25 30

Arg Gly Ile Arg Glu Ala Ala Lys Val Leu Asp Lys Arg Gln Ala His
 35 40 45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Met Tyr Val Lys Leu
 50 55 60

Val Glu Ala Leu Cys Ala Glu His Gln Ile Asn Leu Ile Lys Val Asp
65 70 75 80

Asp Asn Lys Lys Leu Gly Glu Trp Val Gly Leu Cys Lys Ile Asp Arg
85 90 95

Glu Gly Lys Pro His Lys Val Val Gly Tyr Ser Cys Val Val Val Lys
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Asp Tyr Gly Lys Glu Ser Gln Ala Lys Asp Val Ile Glu Glu Tyr Phe
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Lys Cys Lys Lys
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<210> 36
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<400> 36

Met Ala Glu Glu Gly Ile Ala Ala Gly Gly Val Met Asp Val Asn Thr
1 5 10 15

Ala Leu Gln Glu Val Leu Lys Thr Ala Leu Ile His Asp Gly Leu Ala
20 25 30

Arg Gly Ile Arg Glu Ala Ala Lys Ala Leu Asp Lys Arg Gln Ala His
35 40 45

Leu Cys Val Leu Ala Ser Asn Cys Asp Glu Pro Met Tyr Val Lys Leu
50 55 60

Val Glu Ala Leu Cys Ala Glu His Gln Ile Asn Leu Ile Lys Val Asp
65 70 75 80

Asp Asn Lys Lys Leu Gly Glu Trp Val Gly Leu Cys Lys Ile Asp Arg
85 90 95

Glu Gly Lys Pro Arg Lys Val Val Gly Cys Ser Cys Val Val Val Lys
100 105 110

Asp Tyr Gly Lys Glu Ser Gln Ala Lys Asp Val Ile Glu Glu Tyr Phe
115 120 125

Lys Cys Lys Lys
130

<210> 37
 <211> 420
 <212> PRT
 <213> Homo sapiens

<400> 37

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Met Thr Met Glu Lys Gly Met Ser Ser Gly Glu Gly Leu Pro Ser Arg
1          5          10          15

Ser Ser Gln Val Ser Ala Gly Lys Ile Thr Ala Lys Glu Leu Glu Thr
          20          25          30

Lys Gln Ser Tyr Lys Glu Lys Arg Gly Gly Phe Val Leu Val His Ala
          35          40          45

Gly Ala Gly Tyr His Ser Glu Ser Lys Ala Lys Glu Tyr Lys His Val
          50          55          60

Cys Lys Arg Ala Cys Gln Lys Ala Ile Glu Lys Leu Gln Ala Gly Ala
65          70          75          80

Leu Ala Thr Asp Ala Val Thr Ala Ala Leu Val Glu Leu Glu Asp Ser
          85          90          95

Pro Phe Thr Asn Ala Gly Met Gly Ser Asn Leu Asn Leu Leu Gly Glu
          100          105          110

Ile Glu Cys Asp Ala Ser Ile Met Asp Gly Lys Ser Leu Asn Phe Gly
          115          120          125

Ala Val Gly Ala Leu Ser Gly Ile Lys Asn Pro Val Ser Val Ala Asn
          130          135          140

Arg Leu Leu Cys Glu Gly Gln Lys Gly Lys Leu Ser Ala Gly Arg Ile
145          150          155          160

Pro Pro Cys Phe Leu Val Gly Glu Gly Ala Tyr Arg Trp Ala Val Asp
          165          170          175

His Gly Ile Pro Ser Cys Pro Pro Asn Ile Met Thr Thr Arg Phe Ser
          180          185          190

Leu Ala Ala Phe Lys Arg Asn Lys Arg Lys Leu Glu Leu Ala Glu Arg
          195          200          205

Val Asp Thr Asp Phe Met Gln Leu Lys Lys Arg Arg Gln Ser Ser Glu
210          215          220

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Lys Glu Asn Asp Ser Gly Thr Leu Asp Thr Val Gly Ala Val Val Val
 225 230 235 240
 Asp His Glu Gly Asn Val Ala Ala Ala Val Ser Ser Gly Gly Leu Ala
 245 250 255
 Leu Lys His Pro Gly Arg Val Gly Gln Ala Ala Leu Tyr Gly Cys Gly
 260 265 270
 Cys Trp Ala Glu Asn Thr Gly Ala His Asn Pro Tyr Ser Thr Ala Val
 275 280 285
 Ser Thr Ser Gly Cys Gly Glu His Leu Val Arg Thr Ile Leu Ala Arg
 290 295 300
 Glu Cys Ser His Ala Leu Gln Ala Glu Asp Ala His Gln Ala Leu Leu
 305 310 315 320
 Glu Thr Met Gln Asn Lys Phe Ile Ser Ser Pro Phe Leu Ala Ser Glu
 325 330 335
 Asp Gly Val Leu Gly Gly Val Ile Val Leu Arg Ser Cys Arg Cys Ser
 340 345 350
 Ala Glu Pro Asp Phe Ser Gln Asn Lys Gln Thr Leu Leu Val Glu Phe
 355 360 365
 Leu Trp Ser His Thr Thr Glu Ser Met Cys Val Gly Tyr Met Ser Ala
 370 375 380
 Gln Asp Gly Lys Ala Lys Thr His Ile Ser Arg Leu Pro Pro Gly Ala
 385 390 395 400
 Val Ala Gly Gln Ser Val Ala Ile Glu Gly Gly Val Cys Arg Leu Glu
 405 410 415
 Ser Pro Val Asn
 420
 <210> 38
 <211> 496
 <212> PRT
 <213> Homo sapiens
 <400> 38
 Met Phe Arg Ser Lys Arg Ser Gly Leu Val Arg Arg Leu Trp Arg Ser

1		5		10		15											
Arg	Val	Val	Pro	Asn	Arg	Glu	Glu	Gly	Gly	Ser	Gly	Gly	Gly	Gly	Gly		
			20					25					30				
Gly	Asp	Glu	Asp	Gly	Ser	Leu	Gly	Ser	Arg	Ala	Glu	Pro	Ala	Pro	Arg		
		35					40					45					
Ala	Arg	Glu	Gly	Gly	Gly	Cys	Gly	Arg	Ser	Glu	Val	Arg	Pro	Val	Ala		
		50				55					60						
Pro	Arg	Arg	Pro	Arg	Asp	Ala	Val	Gly	Gln	Arg	Gly	Ala	Gln	Gly	Ala		
65					70					75						80	
Gly	Arg	Arg	Arg	Arg	Ala	Gly	Gly	Pro	Pro	Arg	Pro	Met	Ser	Glu	Pro		
				85					90					95			
Gly	Ala	Gly	Ala	Gly	Ser	Ser	Leu	Leu	Asp	Val	Ala	Glu	Pro	Gly	Gly		
			100					105					110				
Pro	Gly	Trp	Leu	Pro	Glu	Ser	Asp	Cys	Glu	Thr	Val	Thr	Cys	Cys	Leu		
		115					120					125					
Phe	Ser	Glu	Arg	Asp	Ala	Ala	Gly	Ala	Pro	Arg	Asp	Ala	Ser	Asp	Pro		
	130					135					140						
Leu	Ala	Gly	Ala	Ala	Leu	Glu	Pro	Ala	Gly	Gly	Gly	Arg	Ser	Arg	Glu		
145					150					155					160		
Ala	Arg	Ser	Arg	Leu	Leu	Leu	Leu	Glu	Gln	Glu	Leu	Lys	Thr	Val	Thr		
				165					170					175			
Tyr	Ser	Leu	Leu	Lys	Arg	Leu	Lys	Glu	Arg	Ser	Leu	Asp	Thr	Leu	Leu		
			180					185					190				
Glu	Ala	Val	Glu	Ser	Arg	Gly	Gly	Val	Pro	Gly	Gly	Cys	Val	Leu	Val		
		195					200					205					
Pro	Arg	Ala	Asp	Leu	Arg	Leu	Gly	Gly	Gln	Pro	Ala	Pro	Pro	Gln	Leu		
	210					215					220						
Leu	Leu	Gly	Arg	Leu	Phe	Arg	Trp	Pro	Asp	Leu	Gln	His	Ala	Val	Glu		
225					230					235					240		
Leu	Lys	Pro	Leu	Cys	Gly	Cys	His	Ser	Phe	Ala	Ala	Ala	Ala	Asp	Gly		
				245					250					255			

Pro Thr Val Cys Cys Asn Pro Tyr His Phe Ser Arg Leu Cys Gly Pro
 260 265 270
 Glu Ser Pro Pro Pro Pro Tyr Ser Arg Leu Ser Pro Arg Asp Glu Tyr
 275 280 285
 Lys Pro Leu Asp Leu Ser Asp Ser Thr Leu Ser Tyr Thr Glu Thr Glu
 290 295 300
 Ala Thr Asn Ser Leu Ile Thr Ala Pro Gly Glu Phe Ser Asp Ala Ser
 305 310 315 320
 Met Ser Pro Asp Ala Thr Lys Pro Ser His Trp Cys Ser Val Ala Tyr
 325 330 335
 Trp Glu His Arg Thr Arg Val Gly Arg Leu Tyr Ala Val Tyr Asp Gln
 340 345 350
 Ala Val Ser Ile Phe Tyr Asp Leu Pro Gln Gly Ser Gly Phe Cys Leu
 355 360 365
 Gly Gln Leu Asn Leu Glu Gln Arg Ser Glu Ser Val Arg Arg Thr Arg
 370 375 380
 Ser Lys Ile Gly Phe Gly Ile Leu Leu Ser Lys Glu Pro Asp Gly Val
 385 390 395 400
 Trp Ala Tyr Asn Arg Gly Glu His Pro Ile Phe Val Asn Ser Pro Thr
 405 410 415
 Leu Asp Ala Pro Gly Gly Arg Ala Leu Val Val Arg Lys Val Pro Pro
 420 425 430
 Gly Tyr Ser Ile Lys Val Phe Asp Phe Glu Arg Ser Gly Leu Gln His
 435 440 445
 Ala Pro Glu Pro Asp Ala Ala Asp Gly Pro Tyr Asp Pro Asn Ser Val
 450 455 460
 Arg Ile Ser Phe Ala Lys Gly Trp Gly Pro Cys Tyr Ser Arg Gln Phe
 465 470 475 480
 Ile Thr Ser Cys Pro Cys Trp Leu Glu Ile Leu Leu Asn Asn Pro Arg
 485 490 495

<210> 39

<211> 426
 <212> PRT
 <213> Homo sapiens

<400> 39

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Met Phe Arg Thr Lys Arg Ser Ala Leu Val Arg Arg Leu Trp Arg Ser
1          5          10          15

Arg Ala Pro Gly Gly Glu Asp Glu Glu Gly Ala Gly Gly Gly Gly
          20          25          30

Gly Gly Gly Glu Leu Arg Gly Glu Gly Ala Thr Asp Ser Arg Ala His
          35          40          45

Gly Ala Gly Gly Gly Gly Pro Gly Arg Ala Gly Cys Cys Leu Gly Lys
          50          55          60

Ala Val Arg Gly Ala Lys Gly His His His Pro His Pro Pro Ala Ala
65          70          75          80

Gly Ala Gly Ala Ala Gly Gly Ala Glu Ala Asp Leu Lys Ala Leu Thr
          85          90          95

His Ser Val Leu Lys Lys Leu Lys Glu Arg Gln Leu Glu Leu Leu Leu
          100          105          110

Gln Ala Val Glu Ser Arg Gly Gly Thr Arg Thr Ala Cys Leu Leu Leu
          115          120          125

Pro Gly Arg Leu Asp Cys Arg Leu Gly Pro Gly Ala Pro Ala Gly Ala
          130          135          140

Gln Pro Ala Gln Pro Pro Ser Ser Tyr Ser Leu Pro Leu Leu Leu Cys
145          150          155          160

Lys Val Phe Arg Trp Pro Asp Leu Arg His Ser Ser Glu Val Lys Arg
          165          170          175

Leu Cys Cys Cys Glu Ser Tyr Gly Lys Ile Asn Pro Glu Leu Val Cys
          180          185          190

Cys Asn Pro His His Leu Ser Arg Leu Cys Glu Leu Glu Ser Pro Pro
          195          200          205

Pro Pro Tyr Ser Arg Tyr Pro Met Asp Phe Leu Lys Pro Thr Ala Asp
          210          215          220

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Cys Pro Asp Ala Val Pro Ser Ser Ala Glu Thr Gly Gly Thr Asn Tyr
 225 230 235 240

Leu Ala Pro Gly Gly Leu Ser Asp Ser Gln Leu Leu Leu Glu Pro Gly
 245 250 255

Asp Arg Ser His Trp Cys Val Val Ala Tyr Trp Glu Glu Lys Thr Arg
 260 265 270

Val Gly Arg Leu Tyr Cys Val Gln Glu Pro Ser Leu Asp Ile Phe Tyr
 275 280 285

Asp Leu Pro Gln Gly Asn Gly Phe Cys Leu Gly Gln Leu Asn Ser Asp
 290 295 300

Asn Lys Ser Gln Leu Val Gln Lys Val Arg Ser Lys Ile Gly Cys Gly
 305 310 315 320

Ile Gln Leu Thr Arg Glu Val Asp Gly Val Trp Val Tyr Asn Arg Ser
 325 330 335

Ser Tyr Pro Ile Phe Ile Lys Ser Ala Thr Leu Asp Asn Pro Asp Ser
 340 345 350

Arg Thr Leu Leu Val His Lys Val Phe Pro Gly Phe Ser Ile Lys Ala
 355 360 365

Phe Asp Tyr Glu Lys Ala Tyr Ser Leu Gln Arg Pro Asn Asp His Glu
 370 375 380

Phe Met Gln Gln Pro Trp Thr Gly Phe Thr Val Gln Ile Ser Phe Val
 385 390 395 400

Lys Gly Trp Gly Gln Cys Tyr Thr Arg Gln Phe Ile Ser Ser Cys Pro
 405 410 415

Cys Trp Leu Glu Val Ile Phe Asn Ser Arg
 420 425

<210> 40
 <211> 367
 <212> PRT
 <213> Homo sapiens

<400> 40

Met Val Met Glu Val Gly Thr Leu Asp Ala Gly Gly Leu Arg Ala Leu
 1 5 10 15

Leu Gly Glu Arg Ala Ala Gln Cys Leu Leu Leu Asp Cys Arg Ser Phe
 20 25 30

Phe Ala Phe Asn Ala Gly His Ile Ala Gly Ser Val Asn Val Arg Phe
 35 40 45

Ser Thr Ile Val Arg Arg Arg Ala Lys Gly Ala Met Gly Leu Glu His
 50 55 60

Ile Val Pro Asn Ala Glu Leu Arg Gly Arg Leu Leu Ala Gly Ala Tyr
 65 70 75 80

His Ala Val Val Leu Leu Asp Glu Arg Ser Ala Ala Leu Asp Gly Ala
 85 90 95

Lys Arg Asp Gly Thr Leu Ala Leu Ala Ala Gly Ala Leu Cys Arg Glu
 100 105 110

Ala Arg Ala Ala Gln Val Phe Phe Leu Lys Gly Gly Tyr Glu Ala Phe
 115 120 125

Ser Ala Ser Cys Pro Glu Leu Cys Ser Lys Gln Ser Thr Pro Met Gly
 130 135 140

Leu Ser Leu Pro Leu Ser Thr Ser Val Pro Asp Ser Ala Glu Ser Gly
 145 150 155 160

Cys Ser Ser Cys Ser Thr Pro Leu Tyr Asp Gln Gly Gly Pro Val Glu
 165 170 175

Ile Leu Pro Phe Leu Tyr Leu Gly Ser Ala Tyr His Ala Ser Arg Lys
 180 185 190

Asp Met Leu Asp Ala Leu Gly Ile Thr Ala Leu Ile Asn Val Ser Ala
 195 200 205

Asn Cys Pro Asn His Phe Glu Gly His Tyr Gln Tyr Lys Ser Ile Pro
 210 215 220

Val Glu Asp Asn His Lys Ala Asp Ile Ser Ser Trp Phe Asn Glu Ala
 225 230 235 240

Ile Asp Phe Ile Asp Ser Ile Lys Asn Ala Gly Gly Arg Val Phe Val
 245 250 255

His Cys Gln Ala Gly Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr

260 265 270
 Leu Met Arg Thr Asn Arg Val Lys Leu Asp Glu Ala Phe Glu Phe Val
 275 280 285
 Lys Gln Arg Arg Ser Ile Ile Ser Pro Asn Phe Ser Phe Met Gly Gln
 290 295 300
 Leu Leu Gln Phe Glu Ser Gln Val Leu Ala Pro His Cys Ser Ala Glu
 305 310 315 320
 Ala Gly Ser Pro Ala Met Ala Val Leu Asp Arg Gly Thr Ser Thr Thr
 325 330 335
 Thr Val Phe Asn Phe Pro Val Ser Ile Pro Val His Ser Thr Asn Ser
 340 345 350
 Ala Leu Ser Tyr Leu Gln Ser Pro Ile Thr Thr Ser Pro Ser Cys
 355 360 365
 <210> 41
 <211> 314
 <212> PRT
 <213> Homo sapiens
 <400> 41
 Met Gly Leu Glu Ala Ala Arg Glu Leu Glu Cys Ala Ala Leu Gly Thr
 1 5 10 15
 Leu Leu Arg Asp Pro Arg Glu Ala Glu Arg Thr Leu Leu Leu Asp Cys
 20 25 30
 Arg Pro Phe Leu Ala Phe Cys Arg Arg His Val Arg Ala Ala Arg Pro
 35 40 45
 Val Pro Trp Asn Ala Leu Leu Arg Arg Arg Ala Arg Gly Pro Pro Ala
 50 55 60
 Ala Val Leu Ala Cys Leu Leu Pro Asp Arg Ala Leu Arg Thr Arg Leu
 65 70 75 80
 Val Arg Gly Glu Leu Ala Arg Ala Val Val Leu Asp Glu Gly Ser Ala
 85 90 95
 Ser Val Ala Glu Leu Arg Pro Asp Ser Pro Ala His Val Leu Leu Ala
 100 105 110

Ala Leu Leu His Glu Thr Arg Ala Gly Pro Thr Ala Val Tyr Phe Leu
 115 120 125
 Arg Gly Gly Phe Asp Gly Phe Gln Gly Cys Cys Pro Asp Leu Cys Ser
 130 135 140
 Glu Ala Pro Ala Pro Ala Leu Pro Pro Thr Gly Asp Lys Thr Ser Arg
 145 150 155 160
 Ser Asp Ser Arg Ala Pro Val Tyr Asp Gln Gly Gly Pro Val Glu Ile
 165 170 175
 Leu Pro Tyr Leu Phe Leu Gly Ser Cys Ser His Ser Ser Asp Leu Gln
 180 185 190
 Gly Leu Gln Ala Cys Gly Ile Thr Ala Val Leu Asn Val Ser Ala Ser
 195 200 205
 Cys Pro Asn His Phe Glu Gly Leu Phe Arg Tyr Lys Ser Ile Pro Val
 210 215 220
 Glu Asp Asn Gln Met Val Glu Ile Ser Ala Trp Phe Gln Glu Ala Ile
 225 230 235 240
 Gly Phe Ile Asp Trp Val Lys Asn Ser Gly Gly Arg Val Leu Val His
 245 250 255
 Cys Gln Ala Gly Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr Leu
 260 265 270
 Met Gln Ser Arg Arg Val Arg Leu Asp Glu Ala Phe Asp Phe Val Lys
 275 280 285
 Gln Arg Arg Gly Val Ile Ser Pro Asn Phe Ser Phe Met Gly Gln Leu
 290 295 300
 Leu Gln Phe Glu Thr Gln Val Leu Cys His
 305 310
 <210> 42
 <211> 384
 <212> PRT
 <213> Homo sapiens
 <400> 42
 Met Lys Val Thr Ser Leu Asp Gly Arg Gln Leu Arg Lys Met Leu Arg
 1 5 10 15

Lys Glu Ala Ala Ala Arg Cys Val Val Leu Asp Cys Arg Pro Tyr Leu
 20 25 30

Ala Phe Ala Ala Ser Asn Val Arg Gly Ser Leu Asn Val Asn Leu Asn
 35 40 45

Ser Val Val Leu Arg Arg Ala Arg Gly Gly Ala Val Ser Ala Arg Tyr
 50 55 60

Val Leu Pro Asp Glu Ala Ala Arg Ala Arg Leu Leu Gln Glu Gly Gly
 65 70 75 80

Gly Gly Val Ala Ala Val Val Val Leu Asp Gln Gly Ser Arg His Trp
 85 90 95

Gln Lys Leu Arg Glu Glu Ser Ala Ala Arg Val Val Leu Thr Ser Leu
 100 105 110

Leu Ala Cys Leu Pro Ala Gly Pro Arg Val Tyr Phe Leu Lys Gly Gly
 115 120 125

Tyr Glu Thr Phe Tyr Ser Glu Tyr Pro Glu Cys Cys Val Asp Val Lys
 130 135 140

Pro Ile Ser Gln Glu Lys Ile Glu Ser Glu Arg Ala Leu Ile Ser Gln
 145 150 155 160

Cys Gly Lys Pro Val Val Asn Val Ser Tyr Arg Pro Ala Tyr Asp Gln
 165 170 175

Gly Gly Pro Val Glu Ile Leu Pro Phe Leu Tyr Leu Gly Ser Ala Tyr
 180 185 190

His Ala Ser Lys Cys Glu Phe Leu Ala Asn Leu His Ile Thr Ala Leu
 195 200 205

Leu Asn Val Ser Arg Arg Thr Ser Glu Ala Cys Met Thr His Leu His
 210 215 220

Tyr Lys Trp Ile Pro Val Glu Asp Ser His Thr Ala Asp Ile Ser Ser
 225 230 235 240

His Phe Gln Glu Ala Ile Asp Phe Ile Asp Cys Val Arg Glu Lys Gly
 245 250 255

Gly Lys Val Leu Val His Cys Glu Ala Gly Ile Ser Arg Ser Pro Thr

260 265 270
 Ile Cys Met Ala Tyr Leu Met Lys Thr Lys Gln Phe Arg Leu Lys Glu
 275 280 285
 Ala Phe Asp Tyr Ile Lys Gln Arg Arg Ser Met Val Ser Pro Asn Phe
 290 295 300
 Gly Phe Met Gly Gln Leu Leu Gln Tyr Glu Ser Glu Ile Leu Pro Ser
 305 310 315 320
 Thr Pro Asn Pro Gln Pro Pro Ser Cys Gln Gly Glu Ala Ala Gly Ser
 325 330 335
 Ser Leu Ile Gly His Leu Gln Thr Leu Ser Pro Asp Met Gln Gly Ala
 340 345 350
 Tyr Cys Thr Phe Pro Ala Ser Val Leu Ala Pro Val Pro Thr His Ser
 355 360 365
 Thr Val Ser Glu Leu Ser Arg Ser Pro Val Ala Thr Ala Thr Ser Cys
 370 375 380
 <210> 43
 <211> 381
 <212> PRT
 <213> Homo sapiens
 <400> 43
 Met Ile Asp Thr Leu Arg Pro Val Pro Phe Ala Ser Glu Met Ala Ile
 1 5 10 15
 Ser Lys Thr Val Ala Trp Leu Asn Glu Gln Leu Glu Leu Gly Asn Glu
 20 25 30
 Arg Leu Leu Leu Met Asp Cys Arg Pro Gln Glu Leu Tyr Glu Ser Ser
 35 40 45
 His Ile Glu Ser Ala Ile Asn Val Ala Ile Pro Gly Ile Met Leu Arg
 50 55 60
 Arg Leu Gln Lys Gly Asn Leu Pro Val Arg Ala Leu Phe Thr Arg Gly
 65 70 75 80
 Glu Asp Arg Asp Arg Phe Thr Arg Arg Cys Gly Thr Asp Thr Val Val
 85 90 95

Leu Tyr Asp Glu Ser Ser Ser Asp Trp Asn Glu Asn Thr Gly Gly Glu
 100 105 110

Ser Leu Leu Gly Leu Leu Leu Lys Lys Leu Lys Asp Glu Gly Cys Arg
 115 120 125

Ala Phe Tyr Leu Glu Gly Gly Phe Ser Lys Phe Gln Ala Glu Phe Ser
 130 135 140

Leu His Cys Glu Thr Asn Leu Asp Gly Ser Cys Ser Ser Ser Ser Pro
 145 150 155 160

Pro Leu Pro Val Leu Gly Leu Gly Gly Leu Arg Ile Ser Ser Asp Ser
 165 170 175

Ser Ser Asp Ile Glu Ser Asp Leu Asp Arg Asp Pro Asn Ser Ala Thr
 180 185 190

Asp Ser Asp Gly Ser Pro Leu Ser Asn Ser Gln Pro Ser Phe Pro Val
 195 200 205

Glu Ile Leu Pro Phe Leu Tyr Leu Gly Cys Ala Lys Asp Ser Thr Asn
 210 215 220

Leu Asp Val Leu Glu Glu Phe Gly Ile Lys Tyr Ile Leu Asn Val Thr
 225 230 235 240

Pro Asn Leu Pro Asn Leu Phe Glu Asn Ala Gly Glu Phe Lys Tyr Lys
 245 250 255

Gln Ile Pro Ile Ser Asp His Trp Ser Gln Asn Leu Ser Gln Phe Phe
 260 265 270

Pro Glu Ala Ile Ser Phe Ile Asp Glu Ala Arg Gly Lys Asn Cys Gly
 275 280 285

Val Leu Val His Cys Leu Ala Gly Ile Ser Arg Ser Val Thr Val Thr
 290 295 300

Val Ala Tyr Leu Met Gln Lys Leu Asn Leu Ser Met Asn Asp Ala Tyr
 305 310 315 320

Asp Ile Val Lys Met Lys Lys Ser Asn Ile Ser Pro Asn Phe Asn Phe
 325 330 335

Met Gly Gln Leu Leu Asp Phe Glu Arg Thr Leu Gly Leu Ser Ser Pro
 340 345 350

Cys Asn Asn Arg Val Pro Ala Gln Gln Leu Tyr Phe Thr Thr Pro Ser
 355 360 365

Asn Gln Asn Val Tyr Gln Val Asp Ser Leu Gln Ser Thr
 370 375 380

<210> 44
 <211> 419
 <212> PRT
 <213> Homo sapiens

<400> 44

Met Lys Asn Gln Leu Arg Gly Pro Pro Ala Arg Ala His Met Ser Thr
 1 5 10 15

Ser Gly Ala Ala Ala Ala Gly Gly Thr Arg Ala Gly Ser Glu Pro Gly
 20 25 30

Ala Gly Ser Gly Ser Gly Ala Gly Thr Gly Ala Gly Ala Ala Thr Gly
 35 40 45

Ala Gly Ala Met Pro Cys Lys Ser Ala Glu Trp Leu Gln Glu Glu Leu
 50 55 60

Glu Ala Arg Gly Gly Ala Ser Leu Leu Leu Leu Asp Cys Arg Pro His
 65 70 75 80

Glu Leu Phe Glu Ser Ser His Ile Glu Thr Ala Ile Asn Leu Ala Ile
 85 90 95

Pro Gly Leu Met Leu Arg Arg Leu Arg Lys Gly Asn Leu Pro Ile Arg
 100 105 110

Ser Ile Ile Pro Asn His Ala Asp Lys Glu Arg Phe Ala Thr Arg Cys
 115 120 125

Lys Ala Ala Thr Val Leu Leu Tyr Asp Glu Ala Thr Ala Glu Trp Gln
 130 135 140

Pro Glu Pro Gly Ala Pro Ala Ser Val Leu Gly Leu Leu Leu Gln Lys
 145 150 155 160

Leu Arg Asp Asp Gly Cys Gln Ala Tyr Tyr Leu Gln Gly Gly Phe Asn
 165 170 175

Lys Phe Gln Thr Glu Tyr Ser Glu His Cys Glu Thr Asn Val Asp Ser

180										185					190						
Ser	Ser	Ser	Pro	Ser	Ser	Ser	Pro	Pro	Thr	Ser	Val	Leu	Gly	Leu	Gly						
		195					200					205									
Gly	Leu	Arg	Ile	Ser	Ser	Asp	Cys	Ser	Asp	Gly	Glu	Ser	Asp	Arg	Glu						
	210					215					220										
Leu	Pro	Ser	Ser	Ala	Thr	Glu	Ser	Asp	Gly	Ser	Pro	Val	Pro	Ser	Ser						
225					230					235					240						
Gln	Pro	Ala	Phe	Pro	Val	Gln	Ile	Leu	Pro	Tyr	Leu	Tyr	Leu	Gly	Cys						
				245					250					255							
Ala	Lys	Asp	Ser	Thr	Asn	Leu	Asp	Val	Leu	Gly	Lys	Tyr	Gly	Ile	Lys						
			260					265					270								
Tyr	Ile	Leu	Asn	Val	Thr	Pro	Asn	Leu	Pro	Asn	Ala	Phe	Glu	His	Gly						
	275						280					285									
Gly	Glu	Phe	Thr	Tyr	Lys	Gln	Ile	Pro	Ile	Ser	Asp	His	Trp	Ser	Gln						
	290					295					300										
Asn	Leu	Ser	Gln	Phe	Phe	Pro	Glu	Ala	Ile	Ser	Phe	Ile	Asp	Glu	Ala						
305					310					315					320						
Arg	Ser	Lys	Lys	Cys	Gly	Val	Leu	Val	His	Cys	Leu	Ala	Gly	Ile	Ser						
				325					330					335							
Arg	Ser	Val	Thr	Val	Thr	Val	Ala	Tyr	Leu	Met	Gln	Lys	Met	Asn	Leu						
			340					345					350								
Ser	Leu	Asn	Asp	Ala	Tyr	Asp	Phe	Val	Lys	Arg	Lys	Lys	Ser	Asn	Ile						
		355					360					365									
Ser	Pro	Asn	Phe	Asn	Phe	Met	Gly	Gln	Leu	Leu	Asp	Phe	Glu	Arg	Thr						
	370					375					380										
Leu	Gly	Leu	Ser	Ser	Pro	Cys	Asp	Asn	His	Ala	Ser	Ser	Glu	Gln	Leu						
385					390					395					400						
Tyr	Phe	Ser	Thr	Pro	Thr	Asn	His	Asn	Leu	Phe	Pro	Leu	Asn	Thr	Leu						
				405					410					415							
Glu	Ser	Thr																			

<210> 45
 <211> 625
 <212> PRT
 <213> Homo sapiens

<400> 45

Met Ala Gly Asp Arg Leu Pro Arg Lys Val Met Asp Ala Lys Lys Leu
 1 5 10 15

Ala Ser Leu Leu Arg Gly Gly Pro Gly Gly Pro Leu Val Ile Asp Ser
 20 25 30

Arg Ser Phe Val Glu Tyr Asn Ser Trp His Val Leu Ser Ser Val Asn
 35 40 45

Ile Cys Cys Ser Lys Leu Val Lys Arg Arg Leu Gln Gln Gly Lys Val
 50 55 60

Thr Ile Ala Glu Leu Ile Gln Pro Ala Ala Arg Ser Gln Val Glu Ala
 65 70 75 80

Thr Glu Pro Gln Asp Val Val Val Tyr Asp Gln Ser Thr Arg Asp Ala
 85 90 95

Ser Val Leu Ala Ala Asp Ser Phe Leu Ser Ile Leu Leu Ser Lys Leu
 100 105 110

Asp Gly Cys Phe Asp Ser Val Ala Ile Leu Thr Gly Gly Phe Ala Thr
 115 120 125

Phe Ser Ser Cys Phe Pro Gly Leu Cys Glu Gly Lys Pro Ala Ala Leu
 130 135 140

Leu Pro Met Ser Leu Ser Gln Pro Cys Leu Pro Val Pro Ser Val Gly
 145 150 155 160

Leu Thr Arg Ile Leu Pro His Leu Tyr Leu Gly Ser Gln Lys Asp Val
 165 170 175

Leu Asn Lys Asp Leu Met Thr Gln Asn Gly Ile Ser Tyr Val Leu Asn
 180 185 190

Ala Ser Asn Ser Cys Pro Lys Pro Asp Phe Ile Cys Glu Ser Arg Phe
 195 200 205

Met Arg Val Pro Ile Asn Asp Asn Tyr Cys Glu Lys Leu Leu Pro Trp
 210 215 220

Leu Asp Lys Ser Ile Glu Phe Ile Asp Lys Ala Lys Leu Ser Ser Cys
 225 230 235 240
 Gln Val Ile Val His Cys Leu Ala Gly Ile Ser Arg Ser Ala Thr Ile
 245 250 255
 Ala Ile Ala Tyr Ile Met Lys Thr Met Gly Met Ser Ser Asp Asp Ala
 260 265 270
 Tyr Arg Phe Val Lys Asp Arg Arg Pro Ser Ile Ser Pro Asn Phe Asn
 275 280 285
 Phe Leu Gly Gln Leu Leu Glu Tyr Glu Arg Thr Leu Lys Leu Leu Ala
 290 295 300
 Ala Leu Gln Gly Asp Pro Gly Thr Pro Ser Gly Thr Pro Glu Pro Pro
 305 310 315 320
 Pro Ser Pro Ala Ala Gly Ala Pro Leu Pro Arg Leu Pro Pro Pro Thr
 325 330 335
 Ser Glu Ser Ala Ala Thr Gly Asn Ala Ala Ala Arg Glu Gly Gly Leu
 340 345 350
 Ser Ala Gly Gly Glu Pro Pro Ala Pro Pro Thr Pro Pro Ala Thr Ser
 355 360 365
 Ala Leu Gln Gln Gly Leu Arg Gly Leu His Leu Ser Ser Asp Arg Leu
 370 375 380
 Gln Asp Thr Asn Arg Leu Lys Arg Ser Phe Ser Leu Asp Ile Lys Ser
 385 390 395 400
 Ala Tyr Ala Pro Ser Arg Arg Pro Asp Gly Pro Gly Pro Pro Asp Pro
 405 410 415
 Gly Glu Ala Pro Lys Leu Cys Lys Leu Asp Ser Pro Ser Gly Ala Ala
 420 425 430
 Leu Gly Leu Ser Ser Pro Ser Pro Asp Ser Pro Asp Ala Ala Pro Glu
 435 440 445
 Ala Arg Pro Arg Pro Arg Arg Arg Pro Arg Pro Pro Ala Gly Ser Pro
 450 455 460

Ala Arg Ser Pro Ala His Ser Leu Gly Leu Asn Phe Gly Asp Ala Ala
 465 470 475 480

Arg Gln Thr Pro Arg His Gly Leu Ser Ala Leu Ser Ala Pro Gly Leu
 485 490 495

Pro Gly Pro Gly Gln Pro Ala Gly Pro Gly Ala Trp Ala Pro Pro Leu
 500 505 510

Asp Ser Pro Gly Thr Pro Ser Pro Asp Gly Pro Trp Cys Phe Ser Pro
 515 520 525

Glu Gly Ala Gln Gly Ala Gly Gly Val Leu Phe Ala Pro Phe Gly Arg
 530 535 540

Ala Gly Ala Pro Gly Pro Gly Gly Gly Ser Asp Leu Arg Arg Arg Glu
 545 550 555 560

Ala Ala Arg Ala Glu Pro Arg Asp Ala Arg Thr Gly Trp Pro Glu Glu
 565 570 575

Pro Ala Pro Glu Thr Gln Phe Lys Arg Arg Ser Cys Gln Met Glu Phe
 580 585 590

Glu Glu Gly Met Val Glu Gly Arg Ala Arg Gly Glu Glu Leu Ala Ala
 595 600 605

Leu Gly Lys Gln Ala Ser Phe Ser Gly Ser Val Glu Val Ile Glu Val
 610 615 620

Ser
 625

<210> 46
 <211> 384
 <212> PRT
 <213> Homo sapiens

<400> 46

Met Glu Gly Leu Gly Arg Ser Cys Leu Trp Leu Arg Arg Glu Leu Ser
 1 5 10 15

Pro Pro Arg Pro Arg Leu Leu Leu Leu Asp Cys Arg Ser Arg Glu Leu
 20 25 30

Tyr Glu Ser Ala Arg Ile Gly Gly Ala Leu Ser Val Ala Leu Pro Ala
 35 40 45

Leu Leu Leu Arg Arg Leu Arg Arg Gly Ser Leu Ser Val Arg Ala Leu
 50 55 60

Leu Pro Gly Pro Pro Leu Gln Pro Pro Pro Pro Ala Pro Val Leu Leu
 65 70 75 80

Tyr Asp Gln Gly Gly Gly Arg Arg Arg Arg Gly Glu Ala Glu Ala Glu
 85 90 95

Ala Glu Glu Trp Glu Ala Glu Ser Val Leu Gly Thr Leu Leu Gln Lys
 100 105 110

Leu Arg Glu Glu Gly Tyr Leu Ala Tyr Tyr Leu Gln Gly Gly Phe Ser
 115 120 125

Arg Phe Gln Ala Glu Cys Pro His Leu Cys Glu Thr Ser Leu Ala Gly
 130 135 140

Arg Ala Gly Ser Ser Met Ala Pro Val Pro Gly Pro Val Pro Val Val
 145 150 155 160

Gly Leu Gly Ser Leu Cys Leu Gly Ser Asp Cys Ser Asp Ala Glu Ser
 165 170 175

Glu Ala Asp Arg Asp Ser Met Ser Cys Gly Leu Asp Ser Glu Gly Ala
 180 185 190

Thr Pro Pro Pro Val Gly Leu Arg Ala Ser Phe Pro Val Gln Ile Leu
 195 200 205

Pro Asn Leu Tyr Leu Gly Ser Ala Arg Asp Ser Ala Asn Leu Glu Ser
 210 215 220

Leu Ala Lys Leu Gly Ile Arg Tyr Ile Leu Asn Val Thr Pro Asn Leu
 225 230 235 240

Pro Asn Phe Phe Glu Lys Asn Gly Asp Phe His Tyr Lys Gln Ile Pro
 245 250 255

Ile Ser Asp His Trp Ser Gln Asn Leu Ser Arg Phe Phe Pro Glu Ala
 260 265 270

Ile Glu Phe Ile Asp Glu Ala Leu Ser Gln Asn Cys Gly Val Leu Val
 275 280 285

His Cys Leu Ala Gly Val Ser Arg Ser Val Thr Val Thr Val Ala Tyr

290 295 300
 Leu Met Gln Lys Leu His Leu Ser Leu Asn Asp Ala Tyr Asp Leu Val
 305 310 315 320
 Lys Arg Lys Lys Ser Asn Ile Ser Pro Asn Phe Asn Phe Met Gly Gln
 325 330 335
 Leu Leu Asp Phe Glu Arg Ser Leu Arg Leu Glu Glu Arg His Ser Gln
 340 345 350
 Glu Gln Gly Ser Gly Gly Gln Ala Ser Ala Ala Ser Asn Pro Pro Ser
 355 360 365
 Phe Phe Thr Thr Pro Thr Ser Asp Gly Ala Phe Glu Leu Ala Pro Thr
 370 375 380
 <210> 47
 <211> 303
 <212> PRT
 <213> Homo sapiens
 <400> 47
 Met Gly Arg Lys Val His Ser Asn Gly Ser Gln Phe Ala Glu His Ser
 1 5 10 15
 Arg Ser Pro Arg Arg Thr Gly Arg Asp Cys Lys Pro Val Arg Ala Pro
 20 25 30
 Ser Met Ala Leu Gly Val Ser Gln Leu Ala Gly Arg Ser Arg Cys Leu
 35 40 45
 Cys Ser Glu Ser Gln Gly Gly Tyr Glu Arg Phe Ser Ser Glu Tyr Pro
 50 55 60
 Glu Phe Cys Ser Lys Thr Lys Ala Leu Ala Ala Ile Pro Pro Pro Val
 65 70 75 80
 Pro Pro Ser Ala Thr Glu Pro Leu Asp Leu Gly Cys Ser Ser Cys Gly
 85 90 95
 Thr Pro Leu His Asp Gln Gly Gly Pro Val Glu Ile Leu Pro Phe Leu
 100 105 110
 Tyr Leu Gly Ser Ala Tyr His Ala Ala Arg Arg Asp Met Leu Asp Ala
 115 120 125

Leu Gly Ile Thr Ala Leu Leu Asn Val Ser Ser Asp Cys Pro Asn His
 130 135 140

Phe Glu Gly His Tyr Gln Tyr Lys Cys Ile Pro Val Glu Asp Asn His
 145 150 155 160

Lys Ala Asp Ile Ser Ser Trp Phe Met Glu Ala Ile Glu Tyr Ile Asp
 165 170 175

Ala Val Lys Asp Cys Arg Gly Arg Val Leu Val His Cys Gln Ala Gly
 180 185 190

Ile Ser Arg Ser Ala Thr Ile Cys Leu Ala Tyr Leu Met Met Lys Lys
 195 200 205

Arg Val Arg Leu Glu Glu Ala Phe Glu Phe Val Lys Gln Arg Arg Ser
 210 215 220

Ile Ile Ser Pro Asn Phe Ser Phe Met Gly Gln Leu Leu Gln Phe Glu
 225 230 235 240

Ser Gln Val Leu Ala Thr Ser Cys Ala Ala Glu Ala Ala Ser Pro Ser
 245 250 255

Gly Pro Leu Arg Glu Arg Gly Lys Thr Pro Ala Thr Pro Thr Ser Gln
 260 265 270

Phe Val Phe Ser Phe Pro Val Ser Val Gly Val His Ser Ala Pro Ser
 275 280 285

Ser Leu Pro Tyr Leu His Ser Pro Ile Thr Thr Ser Pro Ser Cys
 290 295 300

<210> 48
 <211> 330
 <212> PRT
 <213> Homo sapiens

<400> 48

Met Ala Ala Val Asp Ser Phe Tyr Leu Leu Tyr Arg Glu Ile Ala Arg
 1 5 10 15

Ser Cys Asn Cys Tyr Met Glu Ala Leu Ala Leu Val Gly Ala Trp Tyr
 20 25 30

Thr Ala Arg Lys Ser Ile Thr Val Ile Cys Asp Phe Tyr Ser Leu Ile
 35 40 45

Arg Leu His Phe Ile Pro Arg Leu Gly Ser Arg Ala Asp Leu Ile Lys
 50 55 60

Gln Tyr Gly Arg Trp Ala Val Val Ser Gly Ala Thr Asp Gly Ile Gly
 65 70 75 80

Lys Ala Tyr Ala Glu Glu Leu Ala Ser Arg Gly Leu Asn Ile Ile Leu
 85 90 95

Ile Ser Arg Asn Glu Glu Lys Leu Gln Val Val Ala Lys Asp Ile Ala
 100 105 110

Asp Thr Tyr Lys Val Glu Thr Asp Ile Ile Val Ala Asp Phe Ser Ser
 115 120 125

Gly Arg Glu Ile Tyr Leu Pro Ile Arg Glu Ala Leu Lys Asp Lys Asp
 130 135 140

Val Gly Ile Leu Val Asn Asn Val Gly Val Phe Tyr Pro Tyr Pro Gln
 145 150 155 160

Tyr Phe Thr Gln Leu Ser Glu Asp Lys Leu Trp Asp Ile Ile Asn Val
 165 170 175

Asn Ile Ala Ala Ala Ser Leu Met Val His Val Val Leu Pro Gly Met
 180 185 190

Val Glu Arg Lys Lys Gly Ala Ile Val Thr Ile Ser Ser Gly Ser Cys
 195 200 205

Cys Lys Pro Thr Pro Gln Leu Ala Ala Phe Ser Ala Ser Lys Ala Tyr
 210 215 220

Leu Asp His Phe Ser Arg Ala Leu Gln Tyr Glu Tyr Ala Ser Lys Gly
 225 230 235 240

Ile Phe Val Gln Ser Leu Ile Pro Phe Tyr Val Ala Thr Ser Met Thr
 245 250 255

Ala Pro Ser Asn Phe Leu His Arg Cys Ser Trp Leu Val Pro Ser Pro
 260 265 270

Lys Val Tyr Ala His His Ala Val Ser Thr Leu Gly Ile Ser Lys Arg
 275 280 285

Thr Thr Gly Tyr Trp Ser His Ser Ile Gln Phe Leu Phe Ala Gln Tyr

290 295 300
 Met Pro Glu Trp Leu Trp Val Trp Gly Ala Asn Ile Leu Asn Arg Ser
 305 310 315 320

 Leu Arg Lys Glu Ala Leu Cys Cys Thr Ala
 325 330

 <210> 49
 <211> 668
 <212> PRT
 <213> Homo sapiens

 <400> 49

 Met Ala Glu Pro Leu Leu Arg Lys Thr Phe Ser Arg Leu Arg Gly Arg
 1 5 10 15

 Glu Lys Leu Pro Arg Lys Lys Ser Asp Ala Lys Glu Arg Gly Pro Gly
 20 25 30

 Val Pro Gly Thr Gly Glu Pro Ala Gly Glu Ile Trp Tyr Asn Pro Ile
 35 40 45

 Pro Glu Glu Asp Pro Arg Pro Pro Ala Pro Glu Pro Pro Gly Pro Gln
 50 55 60

 Pro Gly Ser Ala Glu Ser Glu Gly Leu Ala Pro Gln Gly Ala Ala Pro
 65 70 75 80

 Ala Ser Pro Pro Thr Lys Ala Ser Arg Thr Lys Ser Pro Gly Pro Ala
 85 90 95

 Arg Arg Leu Ser Ile Lys Met Lys Lys Leu Pro Glu Leu Arg Arg Arg
 100 105 110

 Leu Ser Leu Arg Gly Pro Arg Ala Gly Arg Glu Arg Glu Arg Ala Ala
 115 120 125

 Pro Ala Gly Ser Val Ile Ser Arg Tyr His Leu Asp Ser Ser Val Gly
 130 135 140

 Gly Pro Gly Pro Ala Ala Gly Pro Gly Gly Thr Arg Ser Pro Arg Ala
 145 150 155 160

 Gly Tyr Leu Ser Asp Gly Asp Ser Pro Glu Arg Pro Ala Gly Pro Pro
 165 170 175

Ser Pro Thr Ser Phe Arg Pro Tyr Glu Val Gly Pro Ala Ala Arg Ala
 180 185 190

Pro Pro Ala Ala Leu Trp Gly Arg Leu Ser Leu His Leu Tyr Gly Leu
 195 200 205

Gly Gly Leu Arg Pro Ala Pro Gly Ala Thr Pro Arg Asp Leu Cys Cys
 210 215 220

Leu Leu Gln Val Asp Gly Glu Ala Arg Ala Arg Thr Gly Pro Leu Arg
 225 230 235 240

Gly Gly Pro Asp Phe Leu Arg Leu Asp His Thr Phe His Leu Glu Leu
 245 250 255

Glu Ala Ala Arg Leu Leu Arg Ala Leu Val Leu Ala Trp Asp Pro Gly
 260 265 270

Val Arg Arg His Arg Pro Cys Ala Gln Gly Thr Val Leu Leu Pro Thr
 275 280 285

Val Phe Arg Gly Cys Gln Ala Gln Gln Leu Ala Val Arg Leu Glu Pro
 290 295 300

Gln Gly Leu Leu Tyr Ala Lys Leu Thr Leu Ser Glu Gln Gln Glu Ala
 305 310 315 320

Pro Ala Thr Ala Glu Pro Arg Val Phe Gly Leu Pro Leu Pro Leu Leu
 325 330 335

Val Glu Arg Glu Arg Pro Pro Gly Gln Val Pro Leu Ile Ile Gln Lys
 340 345 350

Cys Val Gly Gln Ile Glu Arg Arg Gly Leu Arg Val Val Gly Leu Tyr
 355 360 365

Arg Leu Cys Gly Ser Ala Ala Val Lys Lys Glu Leu Arg Asp Ala Phe
 370 375 380

Glu Arg Asp Ser Ala Ala Val Cys Leu Ser Glu Asp Leu Tyr Pro Asp
 385 390 395 400

Ile Asn Val Ile Thr Gly Ile Leu Lys Asp Tyr Leu Arg Glu Leu Pro
 405 410 415

Thr Pro Leu Ile Thr Gln Pro Leu Tyr Lys Val Val Leu Glu Ala Met
 420 425 430

Ala Arg Asp Pro Pro Asn Arg Val Pro Pro Thr Thr Glu Gly Thr Arg
 435 440 445
 Gly Leu Leu Ser Cys Leu Pro Asp Val Glu Arg Ala Thr Leu Thr Leu
 450 455 460
 Leu Leu Asp His Leu Arg Leu Val Ser Ser Phe His Ala Tyr Asn Arg
 465 470 475 480
 Met Thr Pro Gln Asn Leu Ala Val Cys Phe Gly Pro Val Leu Leu Pro
 485 490 495
 Ala Arg Gln Ala Pro Thr Arg Pro Arg Ala Arg Ser Ser Gly Pro Gly
 500 505 510
 Leu Ala Ser Ala Val Asp Phe Lys His His Ile Glu Val Leu His Tyr
 515 520 525
 Leu Leu Gln Ser Trp Pro Asp Pro Arg Leu Pro Arg Gln Ser Pro Asp
 530 535 540
 Val Ala Pro Tyr Leu Arg Pro Lys Arg Gln Pro Pro Leu His Leu Pro
 545 550 555 560
 Leu Ala Asp Pro Glu Val Val Thr Arg Pro Arg Gly Arg Gly Gly Pro
 565 570 575
 Glu Ser Pro Pro Ser Asn Arg Tyr Ala Gly Asp Trp Ser Val Cys Gly
 580 585 590
 Arg Asp Phe Leu Pro Cys Gly Arg Asp Phe Leu Ser Gly Pro Asp Tyr
 595 600 605
 Asp His Val Thr Gly Ser Asp Ser Glu Asp Glu Asp Glu Glu Val Gly
 610 615 620
 Glu Pro Arg Val Thr Gly Asp Phe Glu Asp Asp Phe Asp Ala Pro Phe
 625 630 635 640
 Asn Pro His Leu Asn Leu Lys Asp Phe Asp Ala Leu Ile Leu Asp Leu
 645 650 655
 Glu Arg Glu Leu Ser Lys Gln Ile Asn Val Cys Leu
 660 665

<210> 50
 <211> 475
 <212> PRT
 <213> Homo sapiens

<400> 50

Met Lys Val Glu Asp Leu Asn Val Cys Glu Pro Ala Ser Pro Ala Pro
 1 5 10 15

Glu Ala Pro Ala Thr Ser Leu Leu Asn Asp Leu Lys Tyr Ser Pro Ser
 20 25 30

Glu Glu Glu Glu Val Thr Tyr Thr Val Ile Asn Gln Phe Gln Gln Lys
 35 40 45

Phe Gly Ala Ala Ile Leu His Ile Lys Lys Gln Asn Val Leu Ser Val
 50 55 60

Ala Ala Glu Gly Ala Asn Val Cys Arg His Gly Lys Leu Cys Trp Leu
 65 70 75 80

Gln Val Ala Thr Asn Cys Arg Val Tyr Leu Phe Asp Ile Phe Leu Leu
 85 90 95

Gly Ser Arg Ala Phe His Asn Gly Leu Gln Met Ile Leu Glu Asp Lys
 100 105 110

Arg Ile Leu Lys Val Ile His Asp Cys Arg Trp Leu Ser Asp Cys Leu
 115 120 125

Ser His Gln Tyr Gly Ile Leu Leu Asn Asn Val Phe Asp Thr Gln Val
 130 135 140

Ala Asp Val Leu Gln Phe Ser Met Glu Thr Gly Gly Tyr Leu Pro Asn
 145 150 155 160

Cys Ile Thr Thr Leu Gln Glu Ser Leu Ile Lys His Leu Gln Val Ala
 165 170 175

Pro Lys Tyr Leu Ser Phe Leu Glu Lys Arg Gln Lys Leu Ile Gln Glu
 180 185 190

Asn Pro Glu Val Trp Phe Ile Arg Pro Val Ser Pro Ser Leu Leu Lys
 195 200 205

Ile Leu Ala Leu Glu Ala Thr Tyr Leu Leu Pro Leu Arg Leu Ala Leu
 210 215 220

Leu Asp Glu Met Met Ser Asp Leu Thr Thr Leu Val Asp Gly Tyr Leu
 225 230 235 240

Asn Thr Tyr Arg Glu Gly Ser Ala Asp Arg Leu Gly Gly Thr Glu Pro
 245 250 255

Thr Cys Met Glu Leu Pro Glu Glu Leu Leu Gln Leu Lys Asp Phe Gln
 260 265 270

Lys Gln Arg Arg Glu Lys Ala Ala Arg Glu Tyr Arg Val Asn Ala Gln
 275 280 285

Gly Leu Leu Ile Arg Thr Val Leu Gln Pro Lys Lys Leu Val Thr Glu
 290 295 300

Thr Ala Gly Lys Glu Glu Lys Val Lys Gly Phe Leu Phe Gly Lys Asn
 305 310 315 320

Phe Arg Ile Asp Lys Ala Pro Ser Phe Thr Ser Gln Asp Phe His Gly
 325 330 335

Asp Val Asn Leu Leu Lys Glu Glu Ser Leu Asn Lys Gln Ala Thr Asn
 340 345 350

Pro Gln His Leu Pro Pro Thr Glu Glu Gly Glu Thr Ser Glu Asp Ser
 355 360 365

Ser Asn Lys Leu Ile Cys Thr Lys Ser Lys Gly Ser Glu Asp Gln Arg
 370 375 380

Ile Thr Gln Lys Glu His Phe Met Thr Pro Lys His Glu Phe Gln Ala
 385 390 395 400

Ser Leu Ser Leu Lys Glu Glu Thr Glu Gln Leu Leu Met Val Glu Asn
 405 410 415

Lys Glu Asp Leu Lys Cys Thr Lys Gln Ala Val Ser Met Ser Ser Phe
 420 425 430

Pro Gln Glu Thr Arg Val Ser Pro Ser Asp Thr Phe Tyr Pro Ile Arg
 435 440 445

Lys Thr Val Val Ser Thr Leu Pro Pro Cys Pro Ala Leu Glu Lys Ile
 450 455 460

Asp Ser Trp Ile Ser Pro Phe Leu Asn Leu Pro

465

470

475

<210> 51
 <211> 1278
 <212> PRT
 <213> Homo sapiens

<400> 51

Met Thr Leu Thr Glu Arg Leu Arg Glu Lys Ile Ser Arg Ala Phe Tyr
 1 5 10 15

Asn His Gly Leu Leu Cys Ala Ser Tyr Pro Ile Pro Ile Ile Leu Phe
 20 25 30

Thr Gly Phe Cys Ile Leu Ala Cys Cys Tyr Pro Leu Leu Lys Leu Pro
 35 40 45

Leu Pro Gly Thr Gly Pro Val Glu Phe Thr Thr Pro Val Lys Asp Tyr
 50 55 60

Ser Pro Pro Pro Val Asp Ser Asp Arg Lys Gln Gly Glu Pro Thr Glu
 65 70 75 80

Gln Pro Glu Trp Tyr Val Gly Ala Pro Val Ala Tyr Val Gln Gln Ile
 85 90 95

Phe Val Lys Ser Ser Val Phe Pro Trp His Lys Asn Leu Leu Ala Val
 100 105 110

Asp Val Phe Arg Ser Pro Leu Ser Arg Ala Phe Gln Leu Val Glu Glu
 115 120 125

Ile Arg Asn His Val Leu Arg Asp Ser Ser Gly Ile Arg Ser Leu Glu
 130 135 140

Glu Leu Cys Leu Gln Val Thr Asp Leu Leu Pro Gly Leu Arg Lys Leu
 145 150 155 160

Arg Asn Leu Leu Pro Glu His Gly Cys Leu Leu Leu Ser Pro Gly Asn
 165 170 175

Phe Trp Gln Asn Asp Trp Glu Arg Phe His Ala Asp Pro Asp Ile Ile
 180 185 190

Gly Thr Ile His Gln His Glu Pro Lys Thr Leu Gln Thr Ser Ala Thr
 195 200 205

Leu Lys Asp Leu Leu Phe Gly Val Pro Gly Lys Tyr Ser Gly Val Ser
 210 215 220
 Leu Tyr Thr Arg Lys Arg Met Val Ser Tyr Thr Ile Thr Leu Val Phe
 225 230 235 240
 Gln His Tyr His Ala Lys Phe Leu Gly Ser Leu Arg Ala Arg Leu Met
 245 250 255
 Leu Leu His Pro Ser Pro Asn Cys Ser Leu Arg Ala Glu Ser Leu Val
 260 265 270
 His Val His Phe Lys Glu Glu Ile Gly Val Ala Glu Leu Ile Pro Leu
 275 280 285
 Val Thr Thr Tyr Ile Ile Leu Phe Ala Tyr Ile Tyr Phe Ser Thr Arg
 290 295 300
 Lys Ile Asp Met Val Lys Ser Lys Trp Gly Leu Ala Leu Ala Ala Val
 305 310 315 320
 Val Thr Val Leu Ser Ser Leu Leu Met Ser Val Gly Leu Cys Thr Leu
 325 330 335
 Phe Gly Leu Thr Pro Thr Leu Asn Gly Gly Glu Ile Phe Pro Tyr Leu
 340 345 350
 Val Val Val Ile Gly Leu Glu Asn Val Leu Val Leu Thr Lys Ser Val
 355 360 365
 Val Ser Thr Pro Val Asp Leu Glu Val Lys Leu Arg Ile Ala Gln Gly
 370 375 380
 Leu Ser Ser Glu Ser Trp Ser Ile Met Lys Asn Met Ala Thr Glu Leu
 385 390 395 400
 Gly Ile Ile Leu Ile Gly Tyr Phe Thr Leu Val Pro Ala Ile Gln Glu
 405 410 415
 Phe Cys Leu Phe Ala Val Val Gly Leu Val Ser Asp Phe Phe Leu Gln
 420 425 430
 Met Leu Phe Phe Thr Thr Val Leu Ser Ile Asp Ile Arg Arg Met Glu
 435 440 445
 Leu Ala Asp Leu Asn Lys Arg Leu Pro Pro Glu Ala Cys Leu Pro Ser
 450 455 460

Ala Lys Pro Val Gly Gln Pro Thr Arg Tyr Glu Arg Gln Leu Ala Val
 465 470 475 480

Arg Pro Ser Thr Pro His Thr Ile Thr Leu Gln Pro Ser Ser Phe Arg
 485 490 495

Asn Leu Arg Leu Pro Lys Arg Leu Arg Val Val Tyr Phe Leu Ala Arg
 500 505 510

Thr Arg Leu Ala Gln Arg Leu Ile Met Ala Gly Thr Val Val Trp Ile
 515 520 525

Gly Ile Leu Val Tyr Thr Asp Pro Ala Gly Leu Arg Asn Tyr Leu Ala
 530 535 540

Ala Gln Val Thr Glu Gln Ser Pro Leu Gly Glu Gly Ala Leu Ala Pro
 545 550 555 560

Met Pro Val Pro Ser Gly Met Leu Pro Pro Ser His Pro Asp Pro Ala
 565 570 575

Phe Ser Ile Phe Pro Pro Asp Ala Pro Lys Leu Pro Glu Asn Gln Thr
 580 585 590

Ser Pro Gly Glu Ser Pro Glu Arg Gly Gly Pro Ala Glu Val Val His
 595 600 605

Asp Ser Pro Val Pro Glu Val Thr Trp Gly Pro Glu Asp Glu Glu Leu
 610 615 620

Trp Arg Lys Leu Ser Phe Arg His Trp Pro Thr Leu Phe Ser Tyr Tyr
 625 630 635 640

Asn Ile Thr Leu Ala Lys Arg Tyr Ile Ser Leu Leu Pro Val Ile Pro
 645 650 655

Val Thr Leu Arg Leu Asn Pro Arg Glu Ala Leu Glu Gly Arg His Pro
 660 665 670

Gln Asp Gly Arg Ser Ala Trp Pro Pro Pro Gly Pro Ile Pro Ala Gly
 675 680 685

His Trp Glu Ala Gly Pro Lys Gly Pro Gly Gly Val Gln Ala His Gly
 690 695 700

Asp Val Thr Leu Tyr Lys Val Ala Ala Leu Gly Leu Ala Thr Gly Ile
 705 710 715 720
 Val Leu Val Leu Leu Leu Cys Leu Tyr Arg Val Leu Cys Pro Arg
 725 730 735
 Asn Tyr Gly Gln Leu Gly Gly Gly Pro Gly Arg Arg Arg Arg Gly Glu
 740 745 750
 Leu Pro Cys Asp Asp Tyr Gly Tyr Ala Pro Pro Glu Thr Glu Ile Val
 755 760 765
 Pro Leu Val Leu Arg Gly His Leu Met Asp Ile Glu Cys Leu Ala Ser
 770 775 780
 Asp Gly Met Leu Leu Val Ser Cys Cys Leu Ala Gly His Val Cys Val
 785 790 795 800
 Trp Asp Ala Gln Thr Gly Asp Cys Leu Thr Arg Ile Pro Arg Pro Gly
 805 810 815
 Gln Arg Arg Asp Ser Gly Val Gly Ser Gly Leu Glu Ala Gln Glu Ser
 820 825 830
 Trp Glu Arg Leu Ser Asp Gly Gly Lys Ala Gly Pro Glu Glu Pro Gly
 835 840 845
 Asp Ser Pro Pro Leu Arg His Arg Pro Arg Gly Pro Pro Pro Pro Ser
 850 855 860
 Leu Phe Gly Asp Gln Pro Asp Leu Thr Cys Leu Ile Asp Thr Asn Phe
 865 870 875 880
 Ser Ala Gln Pro Arg Ser Ser Gln Pro Thr Gln Pro Glu Pro Arg His
 885 890 895
 Arg Ala Val Cys Gly Arg Ser Arg Asp Ser Pro Gly Tyr Asp Phe Ser
 900 905 910
 Cys Leu Val Gln Arg Val Tyr Gln Glu Glu Gly Leu Ala Ala Val Cys
 915 920 925
 Thr Pro Ala Leu Arg Pro Pro Ser Pro Gly Pro Val Leu Ser Gln Ala
 930 935 940
 Pro Glu Asp Glu Gly Gly Ser Pro Glu Lys Gly Ser Pro Ser Leu Ala
 945 950 955 960

Trp Ala Pro Ser Ala Glu Gly Ser Ile Trp Ser Leu Glu Leu Gln Gly
 965 970 975

Asn Leu Ile Val Val Gly Arg Ser Ser Gly Arg Leu Glu Val Trp Asp
 980 985 990

Ala Ile Glu Gly Val Leu Cys Cys Ser Ser Glu Glu Val Ser Ser Gly
 995 1000 1005

Ile Thr Ala Leu Val Phe Leu Asp Lys Arg Ile Val Ala Ala Arg
 1010 1015 1020

Leu Asn Gly Ser Leu Asp Phe Phe Ser Leu Glu Thr His Thr Ala
 1025 1030 1035

Leu Ser Pro Leu Gln Phe Arg Gly Thr Pro Gly Arg Gly Ser Ser
 1040 1045 1050

Pro Ala Ser Pro Val Tyr Ser Ser Ser Asp Thr Val Ala Cys His
 1055 1060 1065

Leu Thr His Thr Val Pro Cys Ala His Gln Lys Pro Ile Thr Ala
 1070 1075 1080

Leu Lys Ala Ala Ala Gly Arg Leu Val Thr Gly Ser Gln Asp His
 1085 1090 1095

Thr Leu Arg Val Phe Arg Leu Glu Asp Ser Cys Cys Leu Phe Thr
 1100 1105 1110

Leu Gln Gly His Ser Gly Ala Ile Thr Thr Val Tyr Ile Asp Gln
 1115 1120 1125

Thr Met Val Leu Ala Ser Gly Gly Gln Asp Gly Ala Ile Cys Leu
 1130 1135 1140

Trp Asp Val Leu Thr Gly Ser Arg Val Ser His Val Phe Ala His
 1145 1150 1155

Arg Gly Asp Val Thr Ser Leu Thr Cys Thr Thr Ser Cys Val Ile
 1160 1165 1170

Ser Ser Gly Leu Asp Asp Leu Ile Ser Ile Trp Asp Arg Ser Thr
 1175 1180 1185

Gly Ile Lys Phe Tyr Ser Ile Gln Gln Asp Leu Gly Cys Gly Ala
 1190 1195 1200

Ser Leu Gly Val Ile Ser Asp Asn Leu Leu Val Thr Gly Gly Gln
 1205 1210 1215

Gly Cys Val Ser Phe Trp Asp Leu Asn Tyr Gly Asp Leu Leu Gln
 1220 1225 1230

Thr Val Tyr Leu Gly Lys Asn Ser Glu Ala Gln Pro Ala Arg Gln
 1235 1240 1245

Ile Leu Val Leu Asp Asn Ala Ala Ile Val Cys Asn Phe Gly Ser
 1250 1255 1260

Glu Leu Ser Leu Val Tyr Val Pro Ser Val Leu Glu Lys Leu Asp
 1265 1270 1275

<210> 52
 <211> 123
 <212> PRT
 <213> Homo sapiens

<400> 52

Met Ile Leu Ala Val His Leu Lys Arg Phe Lys Tyr Met Asp Gln Leu
 1 5 10 15

His Arg Tyr Thr Lys Leu Ser Tyr Arg Val Val Phe Pro Leu Glu Leu
 20 25 30

Arg Leu Phe Asn Thr Ser Gly Asp Ala Thr Asn Pro Asp Arg Met Tyr
 35 40 45

Asp Leu Val Ala Val Val Val His Cys Gly Ser Gly Pro Asn Arg Gly
 50 55 60

His Tyr Ile Ala Ile Val Lys Ser His Asp Phe Trp Leu Leu Phe Asp
 65 70 75 80

Asp Asp Ile Val Glu Lys Ile Asp Thr Gln Ala Ile Glu Glu Phe Tyr
 85 90 95

Gly Leu Thr Ser Asp Thr Gln Arg Thr Leu Ser Leu Val Thr Ser Phe
 100 105 110

Ser Ile Ser Leu Gly Thr Glu Gly Glu Pro Arg
 115 120

<210> 53
 <211> 370
 <212> PRT
 <213> Homo sapiens

<400> 53

Met Glu Ile Leu Met Thr Val Ser Lys Phe Ala Ser Ile Cys Thr Met
 1 5 10 15

Gly Ala Asn Ala Ser Ala Leu Glu Lys Glu Ile Gly Pro Glu Gln Phe
 20 25 30

Pro Val Asn Glu His Tyr Phe Gly Leu Val Asn Phe Gly Asn Thr Cys
 35 40 45

Tyr Cys Asn Ser Val Leu Gln Ala Leu Tyr Phe Cys Arg Pro Phe Arg
 50 55 60

Glu Lys Val Leu Ala Tyr Lys Ser Gln Pro Arg Lys Lys Glu Ser Leu
 65 70 75 80

Leu Thr Cys Leu Ala Asp Leu Phe His Ser Ile Ala Thr Gln Lys Lys
 85 90 95

Lys Val Gly Val Ile Pro Pro Lys Lys Phe Ile Thr Arg Leu Arg Lys
 100 105 110

Glu Asn Glu Leu Phe Asp Asn Tyr Met Gln Gln Asp Ala His Glu Phe
 115 120 125

Leu Asn Tyr Leu Leu Asn Thr Ile Ala Asp Ile Leu Gln Glu Glu Arg
 130 135 140

Lys Gln Glu Lys Gln Asn Gly Arg Leu Pro Asn Gly Asn Ile Asp Asn
 145 150 155 160

Glu Asn Asn Asn Ser Thr Pro Asp Pro Thr Trp Val Asp Glu Ile Phe
 165 170 175

Gln Gly Thr Leu Thr Asn Glu Thr Arg Cys Leu Thr Cys Glu Thr Ile
 180 185 190

Ser Ser Lys Asp Glu Asp Phe Leu Asp Leu Ser Val Asp Val Glu Gln
 195 200 205

Asn Thr Ser Ile Thr His Cys Leu Arg Gly Phe Ser Asn Thr Glu Thr
 210 215 220

Leu Cys Ser Glu Tyr Lys Tyr Tyr Cys Glu Glu Cys Arg Ser Lys Gln
 225 230 235 240

Glu Ala His Lys Arg Met Lys Val Lys Lys Leu Pro Met Ile Leu Ala
 245 250 255

Leu His Leu Lys Arg Phe Lys Tyr Met Asp Gln Leu His Arg Tyr Thr
 260 265 270

Lys Leu Ser Tyr Arg Val Val Phe Pro Leu Glu Leu Arg Leu Phe Asn
 275 280 285

Thr Ser Gly Asp Ala Thr Asn Pro Asp Arg Met Tyr Asp Leu Val Ala
 290 295 300

Val Val Val His Cys Gly Ser Gly Pro Asn Arg Gly His Tyr Ile Ala
 305 310 315 320

Ile Val Lys Ser His Asp Phe Trp Leu Leu Phe Asp Asp Asp Ile Val
 325 330 335

Glu Lys Ile Asp Ala Gln Ala Ile Glu Glu Phe Tyr Gly Leu Thr Ser
 340 345 350

Asp Ile Ser Lys Asn Ser Glu Ser Gly Tyr Ile Leu Phe Tyr Gln Ser
 355 360 365

Arg Asp
 370

<210> 54
 <211> 520
 <212> PRT
 <213> Homo sapiens

<400> 54

Met Gly Pro Gln Arg Arg Leu Ser Pro Ala Gly Ala Ala Leu Leu Trp
 1 5 10 15

Gly Phe Leu Leu Gln Leu Thr Ala Ala Gln Glu Ala Ile Leu His Ala
 20 25 30

Ser Gly Asn Gly Thr Thr Lys Asp Tyr Cys Met Leu Tyr Asn Pro Tyr
 35 40 45

Trp Thr Ala Leu Pro Ser Thr Leu Glu Asn Ala Thr Ser Ile Ser Leu

50		55		60
Met Asn Leu Thr Ser Thr Pro Leu Cys Asn Leu Ser Asp Ile Pro Pro				
65		70		75 80
Val Gly Ile Lys Ser Lys Ala Val Val Val Pro Trp Gly Ser Cys His				
	85		90	95
Phe Leu Glu Lys Ala Arg Ile Ala Gln Lys Gly Gly Ala Glu Ala Met				
	100		105	110
Leu Val Val Asn Asn Ser Val Leu Phe Pro Pro Ser Gly Asn Arg Ser				
	115		120	125
Glu Phe Pro Asp Val Lys Ile Leu Ile Ala Phe Ile Ser Tyr Lys Asp				
	130		135	140
Phe Arg Asp Met Asn Gln Thr Leu Gly Asp Asn Ile Thr Val Lys Met				
145		150		155 160
Tyr Ser Pro Ser Trp Pro Asn Phe Asp Tyr Thr Met Val Val Ile Phe				
	165		170	175
Val Ile Ala Val Phe Thr Val Ala Leu Gly Gly Tyr Trp Ser Gly Leu				
	180		185	190
Val Glu Leu Glu Asn Leu Lys Ala Val Thr Thr Glu Asp Arg Glu Met				
	195		200	205
Arg Lys Lys Lys Glu Glu Tyr Leu Thr Phe Ser Pro Leu Thr Val Val				
	210		215	220
Ile Phe Val Val Ile Cys Cys Val Met Met Val Leu Leu Tyr Phe Phe				
225		230		235 240
Tyr Lys Trp Leu Val Tyr Val Met Ile Ala Ile Phe Cys Ile Ala Ser				
	245		250	255
Ala Met Ser Leu Tyr Asn Cys Leu Ala Ala Leu Ile His Lys Ile Pro				
	260		265	270
Tyr Gly Gln Cys Thr Ile Ala Cys Arg Gly Lys Asn Met Glu Val Arg				
	275		280	285
Leu Ile Phe Leu Ser Gly Leu Cys Ile Ala Val Ala Val Val Trp Ala				
	290		295	300

Val Phe Arg Asn Glu Asp Arg Trp Ala Trp Ile Leu Gln Asp Ile Leu
 305 310 315 320
 Gly Ile Ala Phe Cys Leu Asn Leu Ile Lys Thr Leu Lys Leu Pro Asn
 325 330 335
 Phe Lys Ser Cys Val Ile Leu Leu Gly Leu Leu Leu Leu Tyr Asp Val
 340 345 350
 Phe Phe Val Phe Ile Thr Pro Phe Ile Thr Lys Asn Gly Glu Ser Ile
 355 360 365
 Met Val Glu Leu Ala Ala Gly Pro Phe Gly Asn Asn Glu Lys Leu Pro
 370 375 380
 Val Val Ile Arg Val Pro Lys Leu Ile Tyr Phe Ser Val Met Ser Val
 385 390 395 400
 Cys Leu Met Pro Val Ser Ile Leu Gly Phe Gly Asp Ile Ile Val Pro
 405 410 415
 Gly Leu Leu Ile Ala Tyr Cys Arg Arg Phe Asp Val Gln Thr Gly Ser
 420 425 430
 Ser Tyr Ile Tyr Tyr Val Ser Ser Thr Val Ala Tyr Ala Ile Gly Met
 435 440 445
 Ile Leu Thr Phe Val Val Leu Val Leu Met Lys Lys Gly Gln Pro Ala
 450 455 460
 Leu Leu Tyr Leu Val Pro Cys Thr Leu Ile Thr Ala Ser Val Val Ala
 465 470 475 480
 Trp Arg Arg Lys Glu Met Lys Lys Phe Trp Lys Gly Asn Ser Tyr Gln
 485 490 495
 Met Met Asp His Leu Asp Cys Ala Thr Asn Glu Glu Asn Pro Val Ile
 500 505 510
 Ser Gly Glu Gln Ile Val Gln Gln
 515 520

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International Bureau



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WO 2004/083389 A3

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MBCATS AS MODIFIERS OF THE BETA-CATENIN PATHWAY AND METHODS OF USE

(57) Abstract: Human MBCAT genes are identified as modulators of the beta-catenin pathway, and thus are therapeutic targets for disorders associated with defective beta-catenin function. Methods for identifying modulators of beta-catenin, comprising screening for agents that modulate the activity of MBCAT are provided.



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INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC: G01N 33/566(2006.01);33/53(2006.01);C12Q 1/70(2006.01)

USPC: 436/501;435/5,7.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 436/501; 435/5,7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN DATABASE (cancerlit, biosis, confsci, scisearch, embase, caplus, uspatfull, pctfull, dissabs), WEST, PUBMED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OLOUNI et al Modulation of Wnt3a-Mediated Nuclear Beta-Catenin Accumulation and Activation by Integrin-Linked Kinase in Mammalian Cells. Oncogene. June 26, 2006; [Epub ahead of print], pages 1-11	1-24
A	CLAPPER et al Beta-Catenin-Mediated Signaling: A Molecular Target for Early Chemopreventive Intervention. Mutat Res. November 2004 , Vol. 555, No. 1-2, pages 97-105.	1-24



Further documents are listed in the continuation of Box C.



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24 July 2006 (24.07.2006)

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INTERNATIONAL SEARCH REPORT

International application No.
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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LU et al Isoprenylcysteine Carboxyl Methyltransferase Modulates Endothelial Monolayer Permeability: Involvement of RhoA Carboxyl Methylation. Circ Res. February 2004, Vol. 94, No. 3, pages 306-315.	1-24